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ORAL CONTRACEPTIVE (O.C.) AGENTS

Indications Prevention of pregnancy. *DOSE-RELATED RISK OF THROMBOEMBOLISM.* Because studies have shown a positive association between OC estrogen dose and risk of thromboembolism, it is prudent to minimize estrogen exposure. Prescribe an OC with the least amount of estrogen compatible with an acceptable pregnancy rate and patient acceptance. Start new users on OCs containing 0.05 mg or less of estrogen.

Contraindications 1. Known or suspected pregnancy (see Warning #5). 2. Thrombophlebitis or thromboembolic disorders. 3. Past history of deep vein thrombophlebitis or thromboembolic disorders. 4. Undiagnosed abnormal genital bleeding. 5. OCs should not be used by women who have or have had any of the following: a. cerebral vascular or coronary artery disease, including myocardial infarction. b. known or suspected carcinoma of the breast. c. known or suspected estrogen dependent neoplasia. d. benign or malignant liver tumor that developed during use of OCs or other estrogen containing products.

WARNINGS: Cigarette smoking increases the risk of serious cardiovascular side effects from OC use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use OCs should be strongly advised not to smoke.

The use of OCs is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, liver tumor, gall bladder disease, visual disturbances, fetal abnormalities, and hypertension. Practitioners prescribing OCs should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with OC use is established. One study demonstrated an increased relative risk for fatal venous thromboembolism and several studies demonstrated it for non-fatal venous thromboembolism. They estimate that OC users are 4-11 times more likely than nonusers to develop these diseases without evident cause. One British study reported an excess death rate of 40% in OC users, most of which resulted from cardiovascular disease. Another British study showed a lower death rate in OC users than controls; an increase in cardiovascular deaths was seen but was not statistically significant. A U.S. prospective study failed to disclose increased mortality rates from cardiovascular disorders, but a subset analyzed as a retrospective case-control study showed significant increases in venous thromboembolism. CEREBROVASCULAR DISORDERS. Two American studies demonstrated an increased relative risk for stroke not shown in prior British studies. In an American study of cerebrovascular disorders in women with and without predisposing causes, relative risk of hemorrhagic stroke was estimated as 2.0 times greater and thrombotic stroke as 4-9.5 times greater in users than nonusers. A British long-term follow-up study reported in 1976 a highly significant association between OC use and stroke. Another study had suggested an association in 1974, but the number of cases was too small to estimate the risk. Subarachnoid hemorrhage has been shown to be increased by OC use in British and American studies. Smoking alone increases incidence of these accidents; smoking and pill use appear to increase risk more than either alone.

MYOCARDIAL INFARCTION (MI). Increased relative risk of MI associated with OC use has been reported. One British study found that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing MI, regardless of OC use. OCs were an additional risk factor. In terms of relative risk, it has been estimated that nonsmoking OC users (smoking is considered a major predisposing condition to MI) are twice as likely to have a fatal MI as nonsmoking nonusers. OC users who are smokers have a 5-fold increased risk of fatal infarction compared to nonsmoking users, and a 10-12-fold increased risk compared to nonsmoking nonusers. The number of cigarettes smoked is important. In determining the importance of these relative risks, baseline rates for various age groups must be considered. (Estimates are based on British vital statistics which show acute MI death rates 2-3 times less than in the U.S. so U.S. death rates could be higher.) Importance of other predisposing conditions in determining relative and absolute risks has not been quantified; other synergistic actions may exist. RISK OF DOSE. Using data from several national adverse reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to estrogen dose in OCs. OCs with 0.1 mg or more of estrogen were associated with a higher risk of thromboembolism than those containing 0.05-0.08 mg but quantity of estrogen may not be the sole factor. This was supported by a U.S. study. A British study found a positive association between dose of progestogen or estrogen and certain thromboembolic conditions. Swedish authorities noted decreased reporting of thromboembolic episodes when higher estrogen preparations were no longer prescribed. Careful epidemiological studies to determine degree of thromboembolic disease risk associated with progestogen-only OCs have not been done. Thromboembolic disease has been reported in women using these products, and they should not be considered free of excess risk. PERSISTENCE OF RISK. Two studies have suggested an increased risk may persist for 6 years after discontinuation of OC use for cerebrovascular disease and 9 years for MI; another study suggested the persistence of risk for subarachnoid hemorrhage. ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES. A large British prospective study estimated mortality rate per 100,000 women per year from circulatory system diseases for OC users and nonusers according to age, smoking habits, and duration of use. The overall annual excess death rate for OC users was estimated to be 20/100,000 (ages 15-34–5/100,000; ages 35-44–33/100,000; ages 45-49–140/100,000). Risk is concentrated in long-term users and in smokers, and may persist after OC discontinuation. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all occurred in women 35 or older. An update provided the following rates: ages 15-34–1/6700 for nonsmokers and 1/2000 for smokers; ages 45 and over–1/2500 for nonsmokers and 1/500 for smokers. Risk appeared to increase with parity, but not with duration of use. Until more women under 35 with continuous use for 5 or more years are available, it is not possible to assess relative risk for this age group. Data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. Estimates include combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease for OCs) plus risk attributable to pregnancy or abortion if the method fails (which varies with the effectiveness of the contraceptive method). The study concluded that mortality associated with all contraceptive methods is below that of childbirth, except for OCs in women over 40 who smoke. (Rates given for pill only/smokers for each age are for smokers as a class. For "heavy" smokers (more than 15 cigarettes a day), the rates would be about double; for "light" smokers (less than 15), about half.) The lowest mortality is with the condom or diaphragm backed up by early abortion. The study also concluded that OC users who smoke, especially over 30, have greater mortality risk than OC users who do not smoke.

Risk of thromboembolic and thrombotic disease associated with OCs increases with age after 30 and, for MI is further increased by hypertension, hyperlipidemias, obesity, diabetes, or history of preeclamptic toxemia, and especially by smoking. The following chart gives a gross estimate of risk of death from circulatory disorders associated with OC use.

SMOKING HABITS AND OTHER PREDISPOSING
CONDITIONS–RISK ASSOCIATED WITH USE OF OCs

Age	Below 30	30-39	40+
Heavy smokers	C	B	A
Light smokers	D	C	B
Nonsmokers (no predisposing conditions)	D	C,D	C
Nonsmokers (other predisposing conditions)	C	C,B	B,A

A–Use associated with very high risk.
B–Use associated with high risk.
C–Use associated with moderate risk.
D–Use associated with low risk.

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, discontinue OC immediately. A 4-6 fold increased risk of post-surgery thromboembolic complications has been reported in OC users. If feasible, discontinue OCs at least 4 weeks before surgery associated with increased risk of thromboembolism or prolonged immobilization. Before resuming OC after major surgery or bedrest, balance risks of post-surgery thromboembolic complications with contraceptive needs. Data suggest varicose veins substantially increase risk of superficial venous thrombosis of the leg, the risk depending on the severity of the varicosities. 2. *Ocular Lesions:* Neuro-ocular lesions such as optic neuritis or retinal thrombosis have been associated with OC use. Discontinue OC if there is unexplained, sudden, or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions; and institute appropriate diagnostic and therapeutic measures. 3. *Carcinoma:* Long-term continuous administration of natural or synthetic estrogen in certain animals increases certain tumors, benign or malignant, such as breast, cervix, vagina, uterus, ovary, pituitary and liver. Certain synthetic progestogens, none currently in OCs, increase the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studies reported an increased relative risk (3.1-13.9 times) associating endometrial carcinoma with the prolonged use of estrogens in postmenopausal women. One publication reported the first 30 cases submitted to the registry of cases of adenocarcinoma of the endometrium in women under 40 on OCs. Of the adenocarcinomas found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding when OCs were first given, polycystic ovaries), nearly all occurred in women who had used sequential OCs, which are no longer marketed. No statistical association has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only OCs, although individual cases have been reported. Studies have shown no increased risk of breast cancer to OC or estrogen users. One study found no overall increased risk of breast cancer in OC users but a greater risk was suggested for OC users with documented benign breast disease and for long-term (2-4 years) users. Another study found a history of breast cancer among grandmothers or aunts was significantly more frequent among breast cancer patients who had used an OC continuously for one or more years than among nonusers with breast cancer. One other study indicated an increasing risk of breast cancer in women taking menopausal estrogens, which increased with duration of follow-up. One author suggests that extended (over 6 years) OC use prior to first full term pregnancy was associated with a significant relative risk of breast cancer. A reduced occurrence of benign breast tumors in OC users has been well documented. One study reported malignant melanoma more frequently in OC users than controls and suggests an increased incidence of urinary tract and thyroid cancers. A prospective study of women with cervical dysplasia found an increase in severity and conversion to cancer *in situ* in OC users compared to nonusers. This became statistically significant after 3-4 years of use. Nonreversal of dysplasia within the first 6 months of pill use was suggested to predict progression after prolonged exposure. One study disclosed an increased risk of cancer of the cervix (largely carcinoma *in situ*) in OC users under 40, particularly those who had used OCs over 4 years. There have been other reports of microglandular hyperplasia of the cervix in OC users. One study reported an association between OC use and endocervical adenocarcinoma. In summary, there is no confirmed evidence from human studies of increased risk of cancer associated with OCs. Close clinical surveillance of all OC users is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, take appropriate diagnostic measures to rule out malignancy. Monitor OC users with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms with particular care. 4. *Liver Tumors:* Sudden severe abdominal pain or shock may be due to rupture and hemorrhage of a liver tumor. There have been reports associating benign or malignant liver tumors with short-term and long-term OC use. One study reported use of OCs with high hormonal potency and age over 30 may further increase risk of hepatocellular adenoma. Two studies relate risk with duration of use, risk being much greater after 4 or more years of use. Long-term OC users have an estimated annual incidence of hepatocellular adenoma of 3-4/100,000. Although an uncommon lesion, it should be considered in women presenting with an "acute abdomen". The tumor may cause serious or fatal hemorrhage. Patients with liver tumors have demonstrated variable clinical features which may make preoperative diagnosis difficult. Some cases presented because of right upper quadrant masses, while most had signs and symptoms of acute intraperitoneal hemorrhage. Routine radiological and laboratory studies may not be helpful. Liver scans may show a focal defect. Hepatic arteriography may be useful in diagnosing primary liver neoplasm. 5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring:* Use of female sex hormones–estrogenic and progestational agents–during early pregnancy may seriously damage the offspring. Females exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be of the order of 1/1000 exposures or less. Although there is no evidence that OCs further enhance the risk of developing this type of malignancy, such OC users should be monitored with particular care. A high percentage of women exposed to diethylstilbestrol (30-90%) have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are a precursor of vaginal malignancy. Male children so exposed may develop urogenital tract abnormalities. Although similar data are not available on other estrogens, it cannot be presumed that they would not induce similar changes. Increased risk of congenital anomalies, including heart and limb defects, has been reported following use of sex hormones, including OCs, in pregnancy. One case-control study estimated a 4.7-fold increased relative risk of limb-reduction defects in infants exposed *in utero* to sex hormones (OCs, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some exposures involved only a few days of treatment. Data suggest risk of limb-reduction defects in exposed fetuses is somewhat less than 1/1000 live births. In a large prospective study, cardiovascular defects in children born to women who received female hormones, including OCs, during early pregnancy occurred at 18.2/1000 births, compared to 7.8/1000 for children not so exposed *in utero*. These results are statistically significant. A Welsh study found a statistically significant excess of neural tube defects among offspring of prior OC users (within 3 months) than among controls. The incidence of twin births may be increased for women who conceive shortly after discontinuing OC use. In the past, female sex hormones were used during pregnancy in an attempt to treat threatened or habitual abortion. There is evidence that estrogens are ineffective, and there is no evidence from well controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OCs. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OCs is unknown. If the patient has not adhered to the prescribed schedule, consider possible pregnancy at the first missed period (or 45 days from the last menstrual period if progestogen-only OCs are used) and discontinue OC use until pregnancy has been ruled out. For any patient who has missed two consecutive periods, rule out pregnancy before continuing the OC. If pregnancy is confirmed, tell the patient about potential risks to the fetus and discuss advisability of continuing the pregnancy. Women who discontinue OCs to become pregnant should use an alternate form of contraception for a period of time before attempting to conceive. A 3-month period is supported by a study suggesting increased frequency of neural tube defects in women impregnated during the first 3 months after cessation of OC use. Do not use progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding as a pregnancy test. 6. *Gall Bladder Disease:* Studies report increased risk of gall bladder disease in OC or estrogen users. In one study, an increased risk appeared after 2 years of use and doubled after 4-5 years. In another study, an increased risk was apparent between 6 and 12 months. 7. *Carbohydrate and Lipid Metabolic Effects:* Because a decrease in glucose tolerance has been observed in a significant percentage of patients on OCs, prediabetic and diabetic OC users should be carefully observed. An increase in triglycerides and total phospholipids has been observed in OC users but its clinical significance is unknown. 8. *Elevated Blood Pressure:* An increase in blood pressure has been reported with OC use. Hypertension may occur within a few months of beginning OCs. In the first year of use, incidence of hypertension may be no higher in OC users than in nonusers. Incidence in users increases with exposure and in the fifth year of use is 2.5-3 times that in the first year. Age is strongly correlated with hypertension in OC users. Women with a history of elevated blood pressure (hypertension), preexisting renal disease, history of toxemia or elevated blood pressure during pregnancy, familial tendency to hypertension or its consequences,* or history of excessive weight gain or fluid retention during the menstrual cycle may be more likely to develop elevated blood pressure when given OCs and should be monitored closely. Even though elevated blood pressure may remain within the "normal" range, closely watch elevations, particularly for women with other risk factors for cardiovascular disease or stroke. High blood pressure may or may not persist after OC discontinuation. 9. *Headache:* Discontinue OC and evaluate the cause of onset or exacerbation of migraine or development of a new pattern of headache which is recurrent, persistent, or severe. 10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and missed menses often make users discontinue OCs. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, consider nonfunctional causes. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, use adequate diagnostic measures to rule out pregnancy or malignancy. If pathology has been excluded, time or another formulation may solve the problem. While potentially useful in minimizing menstrual irregularity, change to an OC with a higher estrogen content only if necessary since this may increase the risk of thromboembolic disease. Women with a history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may tend to remain anovulatory or to become amenorrheic after OC discontinuation. Women with these preexisting problems should be advised of this and encouraged to use other contraceptive methods. Post-use anovulation, possibly prolonged, may occur in women without previous irregularities. A higher incidence of galactorrhea and of pituitary tumors (e.g., adenomas) has been associated with amenorrhea in former users compared with nonusers. One study reported a 16-fold increased incidence of pituitary prolactin-secreting tumors among patients with postpill amenorrhea when galactorrhea was present. 11. *Infertility:* There is evidence of impairment of fertility in women discontinuing OCs in comparison with other contraceptive methods, which appears to be independent of duration of use. While impairment diminishes with time, there is an appreciable difference in the results in nulliparous women for OC and other groups 30 months after discontinuation of birth control. For parous women the difference is not apparent 30 months after cessation of contraception. 12. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in OC failure. In progestogen-only OC failures, the ratio of ectopic to intrauterine pregnancies is higher than in nonusers, since the drugs are more effective in preventing intrauterine than ectopic pregnancies. 13. *Breast Feeding:* OCs in the postpartum period may interfere with lactation by decreasing quantity and quality of breast milk. A small fraction of OC hormonal agents has been identified in milk of mothers receiving OCs. Effects, if any, on the breast-fed child have not been determined. If feasible, defer OC use until the infant has been weaned. **Precautions** *GENERAL* 1. Take a complete medical and family history before starting OCs. Pretreatment and periodic physical exams should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant lab tests. As a general rule, OCs should not be prescribed for longer than 1 year without another physical. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may enlarge. 3. Observe patients with a history of psychic depression and discontinue OCs if depression recurs to a serious degree. Patients becoming significantly depressed while taking OCs should stop the OC and use an alternate method of contraception to determine whether the symptom is drug related. 4. OCs may cause some fluid retention. Prescribe with caution, and only with careful monitoring, in patients with conditions that might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma or cardiac, hepatic or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while using OCs. Discontinue OC if jaundice develops. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. OC users may have disturbances in normal tryptophan metabolism that may result in a relative pyridoxine deficiency. The clinical significance is unknown. 8. Serum folate levels may be depressed by OC use. Since the pregnant woman is predisposed to folate deficiency and incidence of folate deficiency increases with increasing gestation, if a woman becomes pregnant shortly after stopping OCs, she may have a greater chance of developing folate deficiency and related complications. 9. Advise the pathologist of OC use when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing OCs. For example: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. f. Increased phospholipids and triglycerides. g. Temporarily decreased glucose tolerance. 11. Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist and temporary or permanent cessation of wear considered. DRUG INTERACTIONS. OCs may be less effective and there may be increased breakthrough bleeding from interactions with rifampin, isoniazid, ampicillin, tetracycline, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, analgesics, tranquilizers, antimigraine preparations, and antihistamines. OCs may alter effectiveness of such other drugs as oral anticoagulants, anticonvulsants, tricyclic antidepressants, antihypertensive agents (e.g., guanethidine), vitamins, hypoglycemic agents, tranquilizers, hypnotic preparations, and theophylline. *CARCINOGENESIS* See Warnings. *PREGNANCY* Pregnancy category X. See Contraindications and Warnings. *NURSING MOTHERS* See Warnings. **Adverse Reactions** An increased risk of the following serious adverse reactions has been associated with OC use (see Warnings): thrombophlebitis, thrombosis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, mesenteric thrombosis, liver tumors, cerebral hemorrhage, hypertension, gall bladder disease, congenital anomalies, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, Raynaud's disease, arterial thromboembolism. The following adverse reactions have been reported in OC users and are believed to be drug related: bleeding irregularities (breakthrough bleeding, spotting, missed menses during treatment, amenorrhea after treatment), gastrointestinal symptoms, (nausea, vomiting, bloating, abdominal cramps), dysmenorrhea, infertility after discontinuance of treatment, edema, chloasma or melasma which may persist after drug is discontinued, breast changes (tenderness, enlargement, and secretion), intolerance to contact lenses, changes in corneal curvature (steepening), change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution of lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, prolactin-secreting pituitary tumors, chilblains. The following adverse reactions have been reported in OC users and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of hair, erythema multiforme, erythema nodosum, hermorrhagic eruptions, vaginitis, porpyhria, impaired renal function, malignant nephrosclerosis (hemolytic uremic syndrome). **Information for the Patient** (See Patient Package Insert).

Revised October 1984

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Contents

May 1
1985

CLINICAL SECTION

Clinical Opinion

Percutaneous umbilical blood sampling 1
John C. Hobbins, M.D., Peter A. Grannum, M.D., Roberto Romero, M.D.,
E. Albert Reece, M.D., and Maurice J. Mahoney, M.D.
New Haven, Connecticut

Clinical Articles

Advanced maternal age: The mature gravida 7
Donna S. Kirz, M.D., Wendy Dorchester, M.P.H., and Roger K. Freeman, M.D.
Long Beach, California

Palliative exenteration—What, when, and why? 12
C. Robert Stanhope, M.D., and Richard E. Symmonds, M.D.
Rochester, Minnesota

(Contents continued on page 7A)

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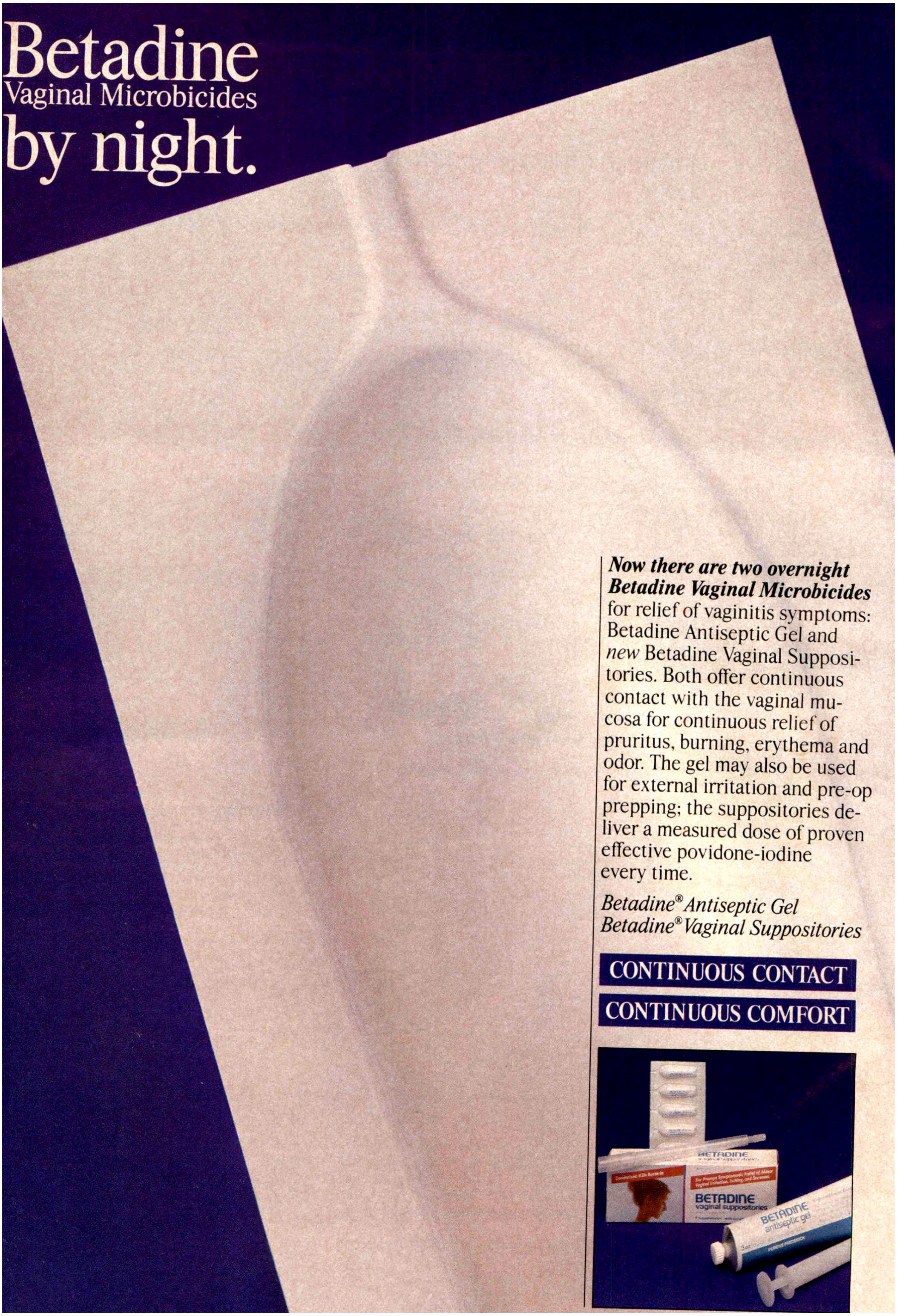

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CONTINUOUS CONTACT

CONTINUOUS COMFORT

Contents continued from page 5A

The importance of primary diagnosis in perinatal death 17
Belinda R. Davies, M.D., and Pedro Arroyo, M.D., M.Sc.
Mexico City, Mexico

Value of a postvoid scan during adnexal sonography 23
Lyndon M. Hill, M.D., and Robert Breckle, R.T., R.D.M.S.
Rochester, Minnesota

Histomorphometry of the human placenta in maternal preeclampsia 25
François Teasdale, M.D.
Montreal, Quebec, Canada

Maternal and perinatal outcome of conservative management of severe preeclampsia in midtrimester 32
Baha M. Sibai, M.D., Mark Taslimi, M.D., Thomas N. Abdella, M.D., and
Todd F. Brooks, M.D., Joseph A. Spinnato, M.D., and Garland D. Anderson, M.D.
Memphis, Tennessee

Urethral isolation of the genital mycoplasmas and *Chlamydia trachomatis* in women with chronic urologic complaints 38
Richard C. Bump, M.D., and William E. Copeland, Jr., M.D.
Columbus, Ohio

Genital tuberculosis in an elderly woman with the primary symptoms of pelvic prolapse: Case report 42
F. J. Montz, M.D., and G. S. diZerega, M.D.
Los Angeles, California

Use of ultrasound in antenatal diagnosis of large-for-gestational age infants in diabetic gravid patients 43
Luis A. Bracero, M.D., Laxmi V. Baxi, M.D., Henry R. Rey, M.S.,
and Ming-Neng Yeh, M.D.
New York, New York

A comparison of sonographic estimation of fetal weight and obstetrically determined gestational age in the prediction of neonatal outcome for the very low-birth weight fetus 47
Frank A. Chervenak, M.D., Gertrud S. Berkowitz, Ph.D., John Thornton, Ph.D.,
Connie Kreiss, M.D., Sharon Youcha, M.D., Richard A. Ehrenkranz, M.D., John C.
Hobbins, M.D., and Richard L. Berkowitz, M.D.
New York, New York

Evaluation of gas-liquid chromatography for the rapid diagnosis of amniotic fluid infection: A preliminary report 51
Gael P. Wager, M.D., M.P.H., Lori S. Hanley, M.T., Harry F. Farb, M.D., and
G. Eric Knox, M.D.
Minneapolis, Minnesota

(Contents continued on page 9A)

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Contents continued from page 7A

Maternal and fetal β-endorphin release in response to the stress of labor and delivery 56
George D. Kofinas, M.D., Alexander D. Kofinas, M.D., and Farangis M. Tavakoli, M.D.
Brooklyn, New York

Methotrexate with citrovorum factor rescue in gestational trophoblastic disease 59
L. C. Wong, M.B., B.S., Y. C. Choo, M.B., B.S., and H. K. Ma, M.B., B.S.
Hong Kong

The amniotic band syndrome: Antenatal sonographic diagnosis and potential pitfalls 63
Barry S. Mahony, M.D., Roy A. Filly, M.D., Peter W. Callen, M.D., and
Mitchell S. Golbus, M.D.
San Francisco, California

Surface changes in intrauterine contraceptive devices after variable use 69
Louis Keith, M.D., Robert Bailey, M.S., Gary S. Berger, M.D., M.S.P.H., and
Michael Method, B.S.
Chicago and DeKalb, Illinois, and Chapel Hill, North Carolina

Plasma dextran levels after abdominal instillation of 32% dextran 70: Evidence for prolonged intraperitoneal retention 78
Robert E. Cleary, M.D., Thomas Howard, D.O., and Gere S. diZerega, M.D.
Indianapolis, Indiana, and Los Angeles, California

Pregnancy complicated by solid-papillary epithelial tumor of the pancreas, pulmonary embolism, and pulmonary embolectomy 80
Patrick Duff, M.D., and Vybert P. Greene, M.D.
San Francisco, California

Elevated maternal α-fetoprotein levels with subsequent fetal exsanguination 82
LeRoy J. Dierker, Jr., M.D.
Cleveland, Ohio

Antenatal therapy with corticosteroids and postpartum complications 83
Luis B. Curet, M.D., John C. Morrison, M.D., A. Vijaya Rao, Ph.D., and the Collaborative
Group on Antenatal Steroid Therapy
Madison, Wisconsin, Research Triangle Park, North Carolina, and Jackson, Mississippi

An arteriovenous malformation in pregnancy: A case report and review of the literature 85
James A. Elliott, M.D., Richard N. Rankin, M.D., Martin J. Inwood, M.D., and
J. Kenneth Milne, M.D.
London, Ontario, Canada

(Contents continued on page 10A)

Contents continued from page 9A

Aminoglycoside dosing in obese puerperal women 89
R. S. Gibbs, M.D., J. D. Blanco, M.D., and K. A. Lipscomb, R.N.
San Antonio, Texas

BASIC SCIENCE SECTION

Exercise dynamics in late gestation: Effects of physical training 91
Mark J. Morton, M.D., Marilyn S. Paul, B.A., Gerry R. Campos, M.D., Mark V. Hart, M.S., and James Metcalfe, M.D.
Portland, Oregon

Implantation site in complete molar pregnancy: A study of immunologically competent cells with monoclonal antibodies 97
Salim E. Kabawat, M.D., Mahpareh Mostoufi-Zadeh, M.D., Ross S. Berkowitz, M.D., Shirley G. Driscoll, M.D., Donald P. Goldstein, M.D., and Atul K. Bhan, M.D.
Boston, Massachusetts

Interferon responses in maternal and fetal mice 99
Arthur T. Evans, M.D., Gloria Carandang, B.S., Edward J. Quilligan, M.D., and Thomas C. Cesario, M.D.
Orange, California

Eutopic and ectopic macromolecular human placental lactogen 103
Ida S. Calvert, Bruce D. Weintraub, Lucy Panton, Lisa Gaffney, and Saul W. Rosen
Bethesda, Maryland

CORRESPONDENCE

Phospholipid analyses in amniotic fluid contaminated by seminal ejaculate D. S. Sheriff *Berka, Benghazi, Libya* 112

Reply Yitzhak Romem, M.D., and Steven H. Golde, M.D. *Los Angeles, California* 112

The management of bradycardia during nonstress tests John D. Yeast, M.D. *Portland, Oregon* 112

Reply John Bourgeois, M.D. *Charlottesville, Virginia* 113

HELLP syndrome: Pathologic entity or technical inadequacy? I. A. Greer, M.B., Ch.B., A. D. Cameron, M.B., Ch.B., and J. J. Walker, M.B., Ch.B. *Glasgow, Scotland* 113

The elusive ellipse D. Christenson, M.D., and R. B. McCown, Ph.D. *Columbus, Ohio* 114

Reply Greggory R. DeVore, M.D. *Los Angeles, California* 115

Contents

Mumps and postmenopausal ovarian cancer Mark H. Schiffman, M.D., M.P.H., Patricia Hartge, Sc.D., Linda P. Lesher, M.H.S., and Larry McGowan, M.D. *Bethesda, Maryland, and Washington, D. C.* 116

Reply Daniel W. Cramer, M.D., Sc.D. *Boston, Massachusetts* 117

BOOKS

Books received 119

ITEMS

Items 120

ERRATUM

Correction of article by Fabro, McLachlan, and Dames 118

Information for authors on pages 23A and 24A

Index to advertisers on page 46A

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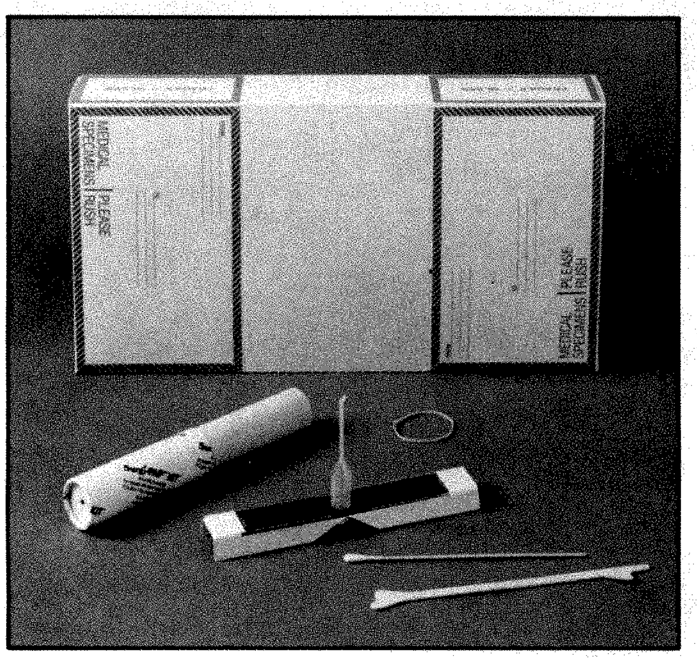
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8 ADVANTAGES IN A FIRST-LINE PARENTERAL ANTIBIOTIC

Infection in the hospitalized patient often calls for the immediate intervention of empiric antibiotic therapy. While awaiting culture and sensitivity results,[*] first-line CEFOBID therapy can provide significant advantages for the patient, the physician, and the hospital:

1. excellent clinical effectiveness[†]
2. the broadest *in vitro*[‡] cephalosporin spectrum—with activity against almost all clinically relevant organisms[§], including *Pseudomonas aeruginosa, Enterococcus,* and *Bacteroides fragilis*
3. high peak serum levels
4. therapeutic concentrations in a variety of tissues and body fluids. Body fluid levels and tissue penetration are regarded as essential to therapeutic efficacy, but specific body fluid and tissue levels have not been correlated with specific therapeutic effects.
5. dual pathway of excretion—no adjustment generally required in usual dosage for patients with renal or hepatic impairment
6. excellent safety profile and well tolerated. CEFOBID is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.
7. *b.i.d.* dosing for all indications—usual adult dosage is 1 to 2 g q12h[¶]
8. substantial administration cost savings because of *b.i.d.* regimen.[1]

CEFOBID® IM/IV q12h

(cefoperazone sodium)

1g and 2g vials

[*] Pending results of susceptibility studies, therapy with CEFOBID may be initiated; however, treatment should be adjusted according to bacteriologic findings.

[†] In infections due to susceptible strains of indicated organisms.

[‡] *In vitro* susceptibility does not necessarily imply a correlation with *in vivo* results.

[§] Based on PDR, 1984; Manufacturer's Prescribing Information.

[¶] In severe infections, or infections caused by less sensitive organisms, the total daily dose and/or frequency *may be* increased. Patients have been successfully treated with a total daily dosage of 6 to 12 grams divided into two, three, or four administrations ranging from 1.5 to 4 grams per dose.

1. Carlin HS, Romankiewicz J: The impact of dosage regimen on intravenous drug cost. Scientific Exhibit, American Society of Hospital Pharmacists, New Orleans, Dec 6-10, 1981.

Please see CEFOBID® brief summary on next page.

CEFOBID *intramuscular use*
(cefoperazone sodium)

CONTRAINDICATIONS: CEFOBID (cefoperazone sodium) is contraindicated in patients with known allergy to the cephalosporin-class of antibiotics.

WARNINGS: BEFORE THERAPY WITH CEFOBID IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

PSEUDOMEMBRANOUS COLITIS HAS BEEN REPORTED WITH THE USE OF CEPHALOSPORINS (AND OTHER BROAD-SPECTRUM ANTIBIOTICS); THEREFORE, IT IS IMPORTANT TO CONSIDER ITS DIAGNOSIS IN PATIENTS WHO DEVELOP DIARRHEA IN ASSOCIATION WITH ANTIBIOTIC USE.

PRECAUTIONS: Although transient elevations of the BUN and serum creatinine have been observed, CEFOBID alone does not appear to cause significant nephrotoxicity. However, concomitant administration of aminoglycosides and other cephalosporins has caused nephrotoxicity.

CEFOBID is extensively excreted in bile. The serum half-life of CEFOBID is increased 2–4 fold in patients with hepatic disease and/or biliary obstruction. In general, total daily dosage above 4 g should not be necessary in such patients. If higher dosages are used, serum concentrations should be monitored.

Because renal excretion is not the main route of elimination of CEFOBID (see CLINICAL PHARMACOLOGY), patients with renal failure require no adjustment in dosage when usual doses are administered. When high doses of CEFOBID are used, concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

The half-life of CEFOBID is reduced slightly during hemodialysis. Thus, dosing should be scheduled to follow a dialysis period. In patients with both hepatic dysfunction and significant renal disease, CEFOBID dosage should not exceed 1–2 g daily without close monitoring of serum concentrations.

As with other antibiotics, vitamin K deficiency has occurred rarely in patients treated with CEFOBID. Those at risk include patients with a poor nutritional status, malabsorption states (e.g., cystic fibrosis), alcoholism, and patients on prolonged hyper-alimentation regimens (administered either intravenously or via a naso-gastric tube). Prothrombin time should be monitored in these patients and exogenous vitamin K administered as indicated.

A disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol (beer, wine) was ingested within 72 hours after CEFOBID administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOBID. A similar reaction has been reported with other cephalosporins.

Prolonged use of CEFOBID may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential.

CEFOBID should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The maximum duration of CEFOBID animal toxicity studies is six months. In none of the *in vivo* or *in vitro* genetic toxicology studies did CEFOBID show any mutagenic potential at either the chromosomal or subchromosomal level. CEFOBID produced no impairment of fertility and had no effects on general reproductive performance or fetal development when administered subcutaneously at daily doses up to 500 to 1000 mg/kg prior to and during mating, and to pregnant female rats during gestation. These doses are 10 to 20 times the estimated usual single clinical dose.

Usage in Pregnancy: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to CEFOBID. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Usage in Nursing Mothers: Only low concentrations of CEFOBID are excreted in human milk. Although CEFOBID passes poorly into breast milk of nursing mothers, caution should be exercised when CEFOBID is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In clinical studies the following adverse effects were observed and were considered to be related to CEFOBID therapy or uncertain etiology:

Hypersensitivity: As with all cephalosporins, hypersensitivity manifested by skin reactions (1 patient in 45), drug fever (1 in 260), or a change in Coombs' test (1 in 60) has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin.

Hematology: As with other beta-lactam antibiotics, reversible neutropenia may occur with prolonged administration. Slight decreases in neutrophil count (1 patient in 50) have been reported. Decreased hemoglobins (1 in 20) or hematocrits (1 in 20) have been reported, which is consistent with published literature on other cephalosporins. Transient eosinophilia has occurred in 1 patient in 10.

Hepatic: Of 1285 patients treated with cefoperazone in clinical trials one patient with a history of liver disease developed significantly elevated liver function enzymes during CEFOBID therapy. Clinical signs and symptoms of nonspecific hepatitis accompanied these increases. After CEFOBID therapy was discontinued, the patient's enzymes returned to pre-treatment levels and the symptomatology resolved. As with other antibiotics that achieve high bile levels, mild transient elevations of liver function enzymes have been observed in 5–10% of the patients receiving CEFOBID therapy. The relevance of these findings, which were not accompanied by overt signs or symptoms of hepatic dysfunction, has not been established.

Gastrointestinal: Diarrhea or loose stools has been reported in 1 in 30 patients. Most of these experiences have been mild or moderate in severity and self-limiting in nature. In all cases, these symptoms responded to symptomatic therapy or ceased when cefoperazone therapy was stopped. Nausea and vomiting have been reported rarely.

Symptoms of pseudomembranous colitis can appear during or for several weeks subsequent to antibiotic therapy (see WARNINGS).

Renal Function Tests: Transient elevations of the BUN (1 in 16) and serum creatinine (1 in 48) have been noted.

Local Reactions: CEFOBID is well tolerated following intramuscular administration. Occasionally, transient pain (1 in 140) may follow administration by this route. When CEFOBID is administered by intravenous infusion some patients may develop phlebitis (1 in 120) at the infusion site.

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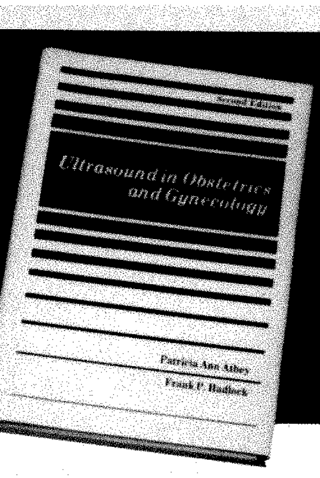

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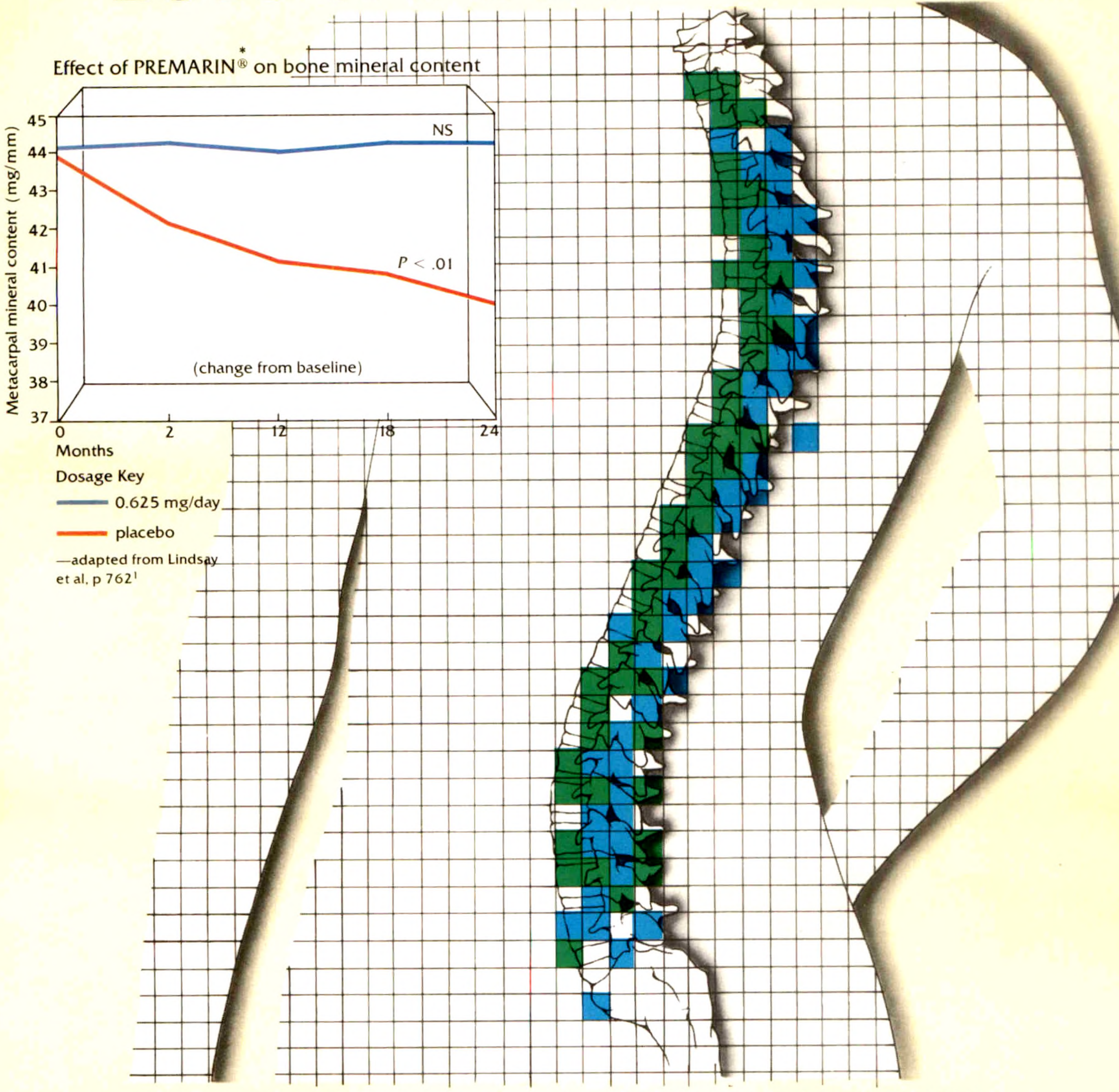
Effect of PREMARIN®* on bone mineral content

Dosage Key

- 0.625 mg/day
- placebo

—adapted from Lindsay et al, p 762[1]

PREMARIN MAY HALT THE DISABLING COURSE OF OSTEOPOROSIS*

Osteoporosis has an enormous epidemiological impact: it affects 10 million American women, and 26% of all women over age 60.[2] The disease begins silently and progresses inexorably for 15 to 20 years, until disabling complications occur.[3]

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*Conjugated Estrogens Tablets have been evaluated as probably effective for estrogen-deficiency-induced osteoporosis.

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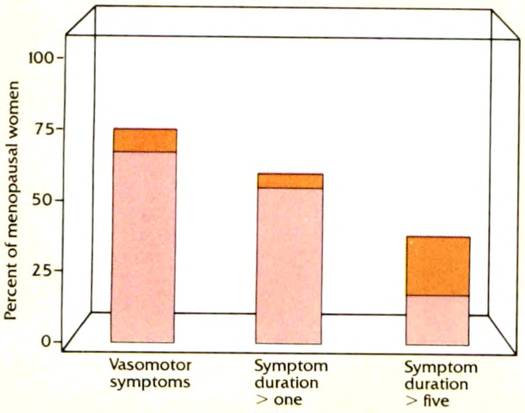
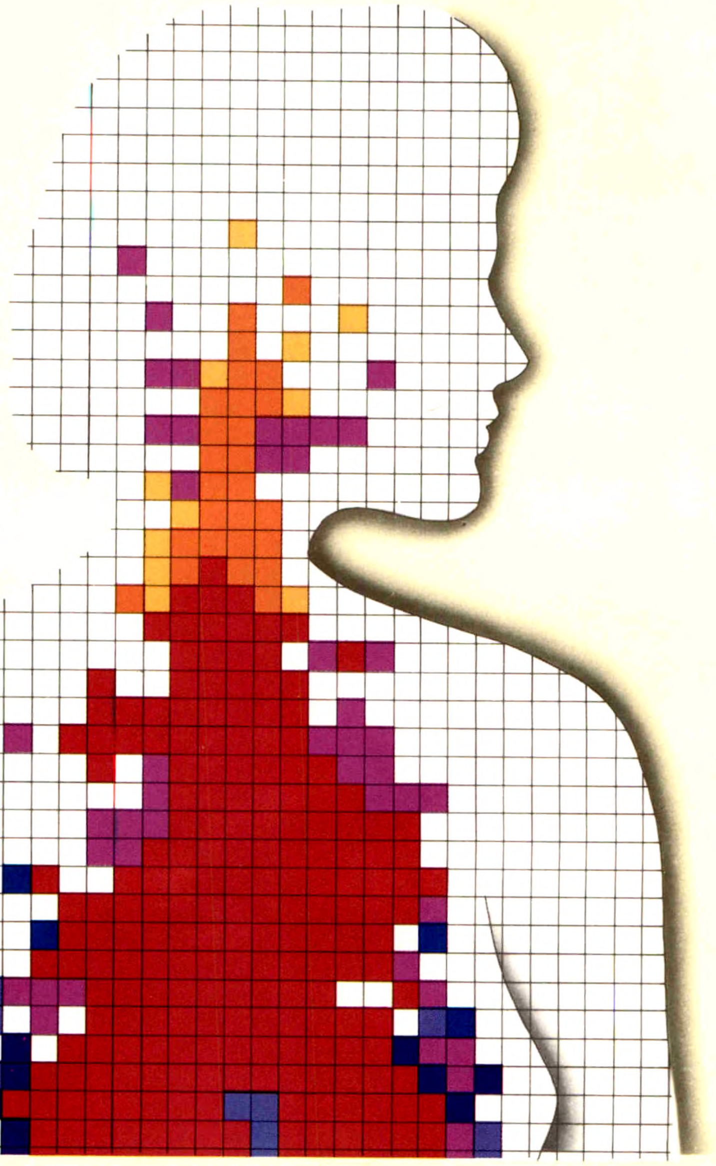
VASOMOTOR SYMPTOMS THAT DEMAND INTERVENTION

Incidence of Vasomotor Symptoms



—adapted from Judd, p 20[4]



PREMARIN RELIEVES MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common manifestation of the menopause, affecting up to 75% of menopausal women. Of these, 80% may suffer for more than a year and up to 50% for more than five years.[4] These symptoms can disrupt a woman's life by chronically interrupting sleep, resulting in anxiety and irritability.

In a study of postmenopausal women suffering severe episodes of cutaneous flushing, symptoms improved markedly after administration of estrogen[5]—the treatment of choice for moderate to severe vasomotor symptoms.[6] The estrogen of choice is PREMARIN, the most widely prescribed estrogen for over 40 years. PREMARIN (Conjugated Estrogens Tablets, U.S.P.) relieves moderate to severe vasomotor symptoms of the natural menopause, as well as the acute and often severe symptoms of surgical menopause.

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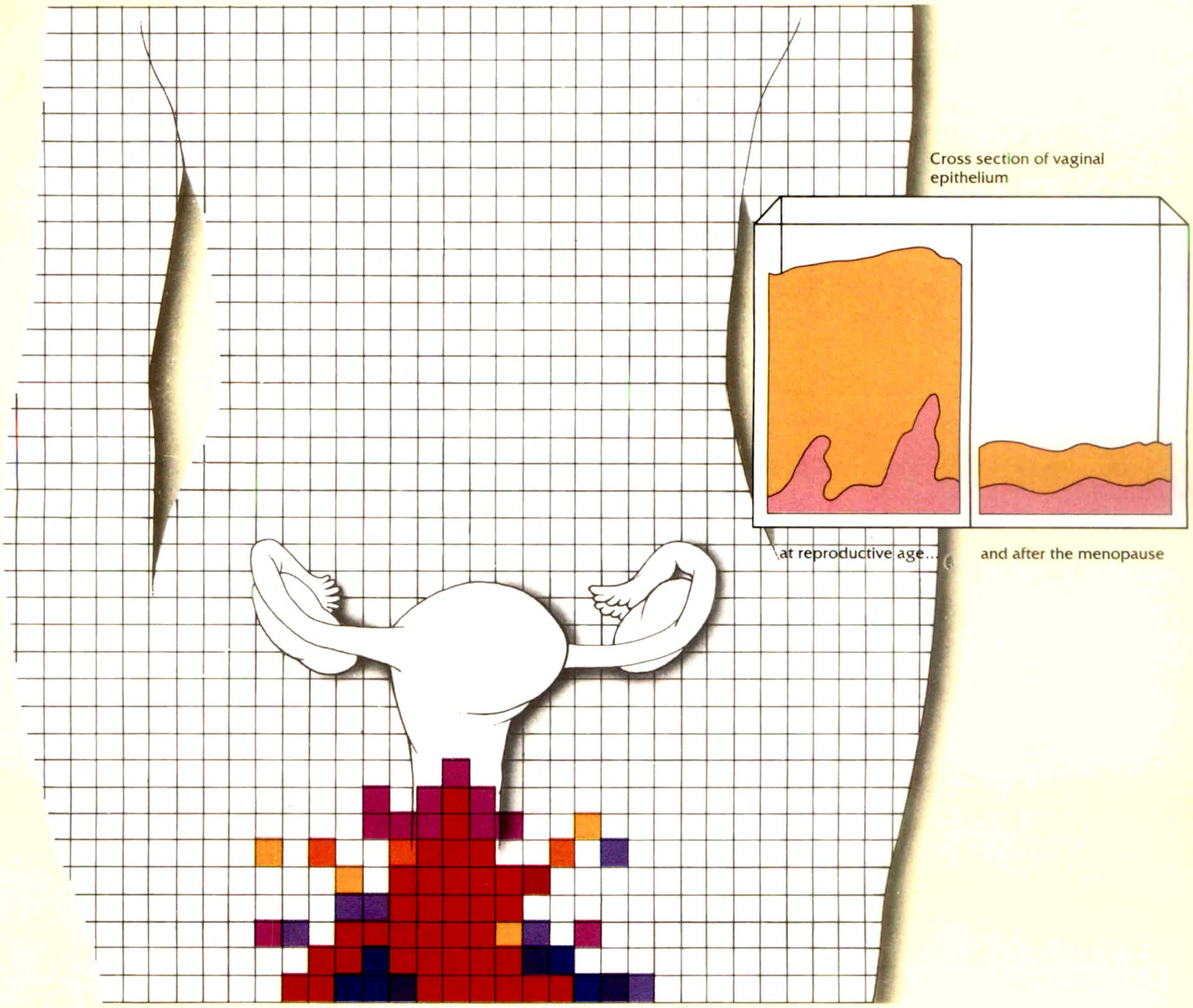

PREMARIN RESTORES THE VAGINAL ENVIRONMENT

In the postmenopausal woman, decreasing levels of estrogen can have devastating effects on a woman's sexual functioning. The pH of vaginal secretions rises, promoting the growth of contaminating organisms. The vaginal epithelium dries and thins, becoming susceptible to irritation, injury, and infection. Sexual relations may be difficult or impossible.

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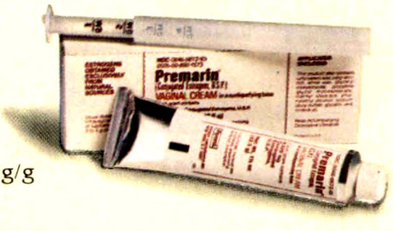

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Please see last page for brief summary of full prescribing information.

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PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream No. 872 Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. **4340R1/285**

References: 1. Lindsay R, Hart DM, Clark DM: The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstet Gynecol* 1984;63:759-763. **2.** Katz WA: *Rheumatic Diseases: Diagnosis and Management.* Philadelphia, JB Lippincott Co, 1977, p 672. **3.** Reese WD: A better way to screen for osteoporosis. *Contemp Ob/Gyn* 1983;22(November):116-131. **4.** Judd HL: After the menopause. *Transition* 1983;1:19-30. **5.** Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. **6.** Meldrum DR: The pathophysiology of postmenopausal symptoms. *Sem Reprod Endocrinol* 1983;1(February):11-17.

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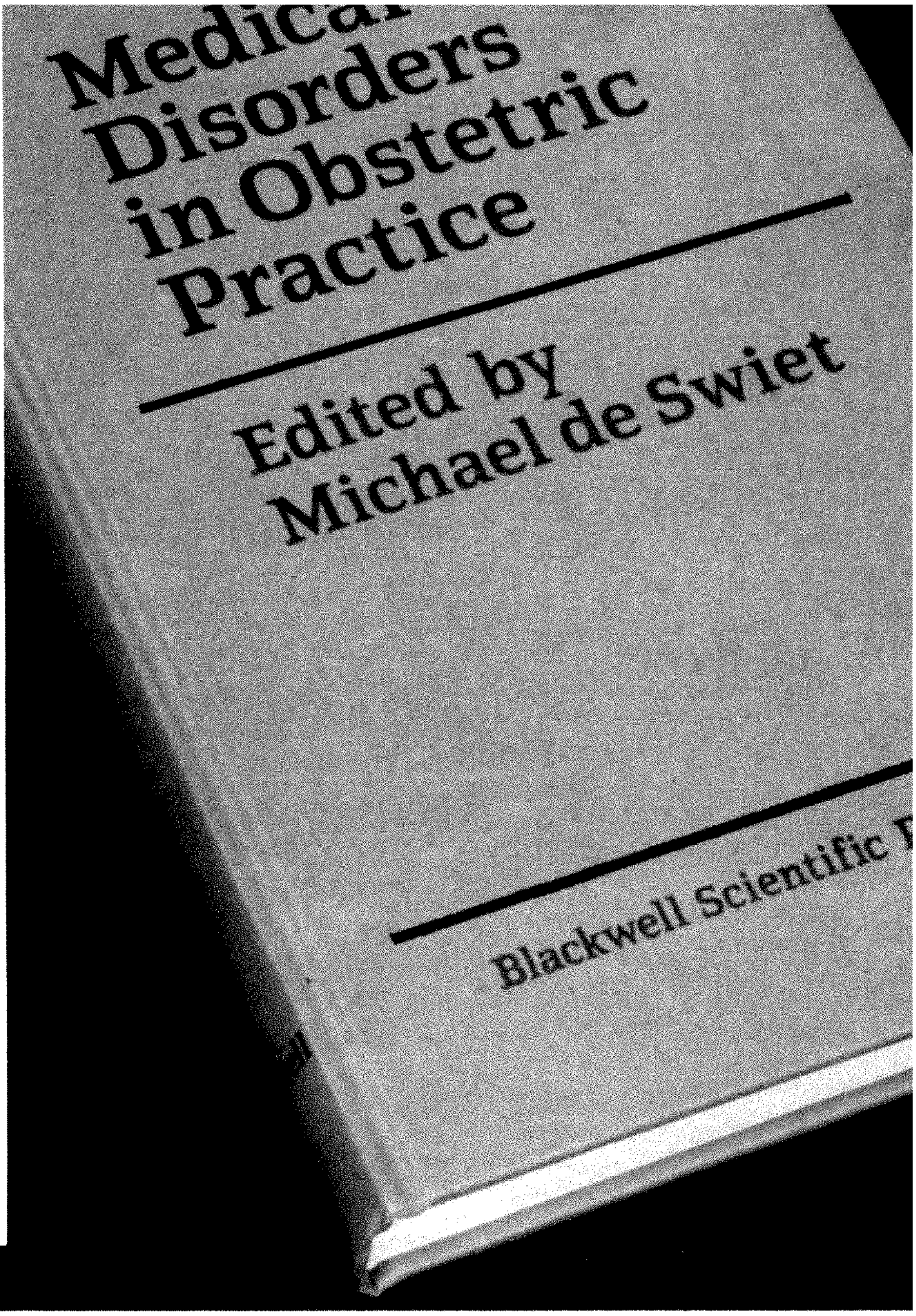

OBSTETRIC PRACTICE

dited by Michael de Swiet, M.D.,
.R.C.P.; with 9 contributors.

'The fact that two lives are at risk, nd the varying physiology during the ourse of pregnancy and post partum nake the bravest of us need a source f help and instruction. The book dited by Michael de Swiet fulfills this ole admirably . . . the book as a vhole is excellent and highly recommended. It is a book to buy." (The ancet)

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The original and two good-quality copies of the manuscript and three glossy prints of illustrations are required.

Manuscripts must be typed double spaced on one side only on 22 by 28 cm (8 1/2 by 11 inch) white bond paper with 1 inch margins at top, bottom, and sides. Number pages consecutively in the upper right-hand corner in the following order: title page, abstract, body of text, references, legends, and tables.

Title page. The title page should contain in sequence the title (concise and suitable for indexing purposes); author line with first name, middle initial, and last name of all authors and their highest academic degree (both M.D. and Ph.D. are acceptable); city(ies), state(s) in which the study was conducted; departmental, divisional, and institutional affiliations at the time the study was performed; acknowledgement of source(s) of support; presented line if applicable; disclaimers, if any; name and address of author to whom requests for reprints should be addressed (if reprints will not be available, it should be so stated); and name and address of author responsible for correspondence concerning the manuscript if different from author to whom reprint requests are addressed. At the bottom of the title page supply a short title for the running head not exceeding 52 characters (including word spaces).

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Text. Do not hesitate to write your manuscript in the first-person, active voice if it is more appropriate to the information you wish to convey. The passive voice is generally more effective for describing techniques or observations since the emphasis is on the "action" rather than the person performing the action.

Only standard abbreviations are to be used. Consult the *Council of Biology Editors Style Manual* or the AMA's *Manual for Authors and Editors*. Abbreviations in the title are not acceptable. They should be avoided, if possible, in the abstract. In the text they should be kept to a practical minimum. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

Either the generic, chemical, or proprietary names of drugs may be used. If the generic or chemical name is used, authors may, if they desire, insert the proprietary name in parentheses after the first mention in the text, with the name of the manufacturer and city and state.

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In the introduction, state concisely the purpose and rationale for the study and cite only the most pertinent references as background.

In the *Material and Methods section* describe briefly (but in sufficient detail to permit other workers to evaluate and reproduce the results) the plan, patients and/or experimental animals and controls, methods and procedures utilized, and statistical method(s) employed.

In the *Results section* present the detailed findings. Include mentions of all tables and/or figures. Avoid duplication of text and supporting material. Emphasize only your important observations; do not compare your observations to those of others. Such comparisons and comments are reserved for the Comment section.

In the *Comment section* state the importance and significance of your findings but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your findings with those of others. No new data should be presented in this section.

Acknowledgements. Acknowledge only persons who have made substantive contributions to the study.

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Illustrations and tables should supplement, not duplicate, the text; presentation in either one or the other will suffice.

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Requirements for special sections

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Current Investigation. Same requirements as for a regular article.

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References:
1. Rössner S et al: *Acta Obstet Gynecol Scand* 59:2
2. Nash AL et al: *Med J Aust* 2:277, 1979. 3. Larsson
et al: *Fertil Steril* 35:172, 1981. 4. Briggs MH: *J Re*
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105:25, 1982.

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IN BRIEF:

Indications and Usage—NORDETTE* is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

> **Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.**
> The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with the use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

PERSISTENCE OF RISK OF VASCULAR DISORDERS—Findings from one study in Britain involving cerebrovascular disease and another in the U.S. concerning MI suggest an increased risk of these conditions in users of OC's persists after discontinuation of the OC's. In the British study, risk of cerebrovascular disease remained elevated in former OC users for at least 6 years after discontinuation. In the U.S. study, increased risk of MI persisted for at least 9 years in women 40 to 49 years old who had used OC's for 5 or more years. Findings in both studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these preexisting problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

Information for the Patient—See Patient Package Labeling.

Laboratory Tests—1. The pathologist should be advised of OC therapy when relevant specimens are submitted.

2. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Decreased pregnanediol excretion.

e. Reduced response to metyrapone test.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates, phenylbutazone phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis, Mutagenesis, Impairment of Fertility—See Warnings section #3, 4, and 5 for information on carcinogenesis, mutagenesis, and impairment of fertility.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings. Because of the potential for adverse reactions in nursing infants from oral contraceptive tablets, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

NORDETTE* each tablet contains
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CLINICAL SECTION

Clinical Opinion

Percutaneous umbilical blood sampling

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New Haven, Connecticut

This report describes a technique for the performance of a sonographically guided percutaneous umbilical blood sampling and its potential uses in the management of diagnostic problems in the second and third trimester of pregnancy. The method has been employed in the prenatal assessment of 13 fetuses at risk for hemostatic failure (hemophilia and idiopathic thrombocytopenic purpura), chromosomal disorders, isoimmunization, and fetal hypoxia. This simple and rapid procedure offers access to the fetal circulation for diagnostic and therapeutic purposes. (AM J OBSTET GYNECOL 1985;152:1-6.)

Key words: Ultrasound, umbilical blood sampling, prenatal assessment

Fetal blood for diagnostic purposes has been traditionally obtained by fetoscopy in the second trimester[1, 2] and fetal scalp sampling[3] in the third trimester. Since fetoscopy carries a 4% to 5% risk[4] of fetal loss and since scalp sampling can only be undertaken in patients in labor with cervical dilatation, these limitations have precluded fetal blood sampling except in special situations. In an effort to overcome these limitations, in 1983 Daffos et al.[5, 6] reported a new technique for obtaining fetal blood, which involved umbilical cord sampling with an ultrasonically guided 20-gauge needle.

Our group has been utilizing a similar technique for sonographically guided percutaneous umbilical blood sampling which involves the use of linear-array ultrasound and a 25-gauge needle. The method was initially used at the time of elective abortion to confirm diagnoses made by amniotic fluid analysis. Once its potential was confirmed, the method was then used diagnostically in the management of various clinical problems in the second and third trimesters.

The purpose of this communication is to describe the technique for percutaneous umbilical blood sampling, to report our diagnostic experience with it, and to discuss its potential uses in various clinical dilemmas of late pregnancy.

Material and methods

The method for percutaneous umbilical blood sampling here described is a modification of the technique for amniocentesis reported by Jeanty et al.[7] The patient is prepared and draped as if an amniocentesis were to be performed. A linear-array transducer (preferably 5 MHz) is placed into a sterile glove. After sterile contact gel is applied to the skin, the operator attempts to identify the umbilical cord near its insertion site in the placenta. By rotating the transducer, one can obtain a view of the long axis of at least 2 cm of umbilical cord at the insertion site (Figs. 1 and 2). Although sampling can be undertaken in this position, it is generally preferable to sample the umbilical cord with a cross-sectional image. To accomplish this, the transducer is carefully rotated 90 degrees so that a cross section of the cord is viewed which is about 1 to 2 cm from its placental insertion (Fig. 3). The operator, holding the transducer in one hand, inserts a 25-gauge spinal needle with the other hand through the skin along side the transducer and advances it by ultrasound guidance through the uterus and into the umbilical vein (Fig. 4). After the stylet is removed, fetal blood is withdrawn into a syringe attached to the hub of the needle while an assistant

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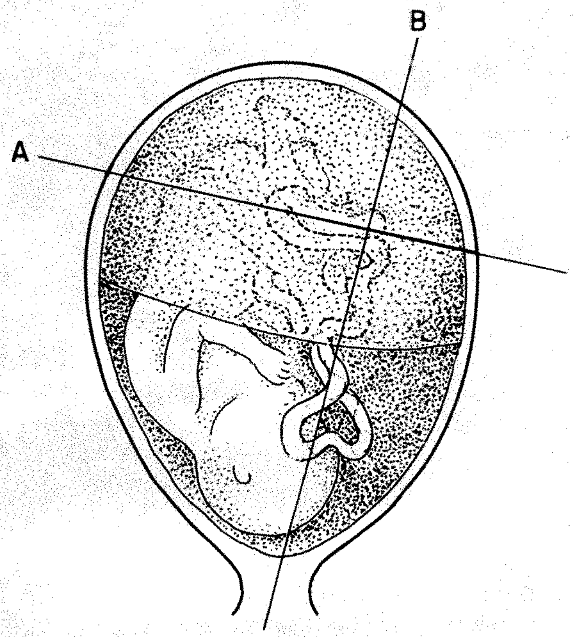

Fig. 1. Schematic demonstrating scanning planes *A* and *B* through the umbilical cord insertion on anterior placenta.

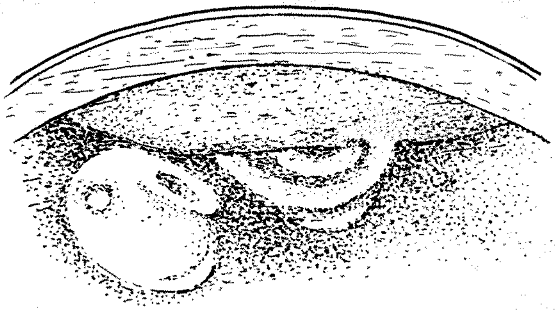

Fig. 2. Schematic demonstrating an examination through scanning plane A, indicating the long axis of the umbilical cord at its insertion on anterior placenta.

continuously visualizes the needle with ultrasound. The syringe may contain a small amount of anticoagulant such as heparin or citrate, or alternatively, the blood can be transferred to a vial with anticoagulant after aspiration (depending upon the test required). Red blood cell size is determined with an electronic cell analyzer (Coulter Electronics, Hialeah, Florida) to distinguish fetal from maternal cells, and a Kleihauer-Betke test is performed later when necessary. However, it should be clear from the ultrasound image when the needle is in the umbilical cord.

If an anterior placenta is encountered, the needle can be visualized throughout its course through the placental substance. With posterior placentas the proposed needle pathway should transverse a fetus-free area between the limbs to the desired puncture site 1 cm from the cord insertion. On occasion fetal movement requires the use of intravenous diazepam, and

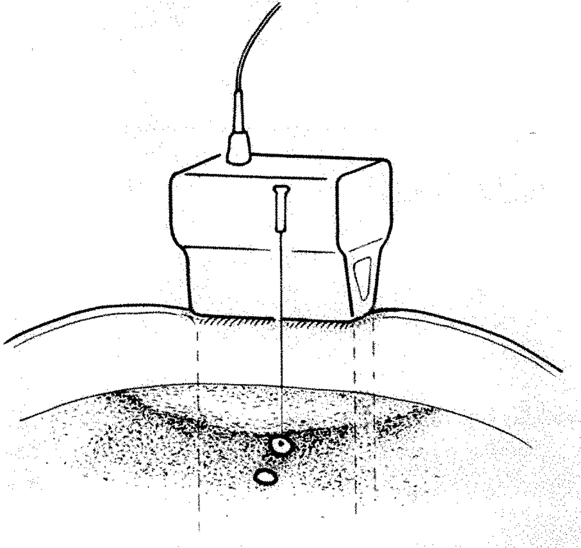

Fig. 3. Schematic demonstrating a sampling plane B through a cross section of the umbilical cord at right angles to plane A.

fetal manipulation and physician patience are necessary to achieve a fetal position that is conducive to fetal blood sampling. In cases of premature rupture of membranes or oligohydramnios, a loop of free cord is chosen that is lodged in a small pocket of fluid.

The particulars of the 13 diagnostic cases are summarized in Table I. Five clinical situations have been chosen to demonstrate the potential of this procedure in the management of the high-risk pregnancy.

Case reports

Case 1: confirmation of equivocal amniotic fluid results. A 43-year-old woman, gravida 1, para 0, was referred at 23 weeks of gestation for prenatal diagnosis. Amniotic fluid analysis from an amniocentesis performed at 17 weeks revealed 60% trisomy 20 cells; the rest were 46,XY. After an attempt at fetoscopy was unsuccessful, she was referred to us for further diagnostic study. Ultrasound examination revealed marked oligohydramnios was present, so it was decided to attempt percutaneous umbilical blood sampling. A sample of fetal blood mixed with amniotic fluid was obtained which revealed a normal karyotype (46,XY) in all 110 cells analyzed. The pregnancy continued uneventfully.

Case 3: hemophilia. A 34-year-old woman, gravida 1, para 0, was referred for percutaneous umbilical blood sampling because she was a documented carrier for hemophilia A and an amniocentesis revealed the fetus to be a male. A fetal sample (mixed with amniotic fluid) revealed normal factor VIII clotting activity and adequate amounts of factor VIII coagulant antigen. The patient's pregnancy was continuing uneventfully 1 week after the sampling procedure.

Case 7: idiopathic thrombocytopenic purpura. A

28-year-old woman, gravida 3, para 2, was diagnosed at 28 weeks of pregnancy to have idiopathic thrombocytopenic purpura. Antiplatelet antibodies were present. On administration of 20 mg of prednisone daily the platelet count was maintained at 64,000. After fetal lung maturity was determined, percutaneous umbilical blood sampling was performed through an anterior placenta at 38.5 weeks, and 2 ml of fetal blood were obtained. The fetal platelet count was 300,000. Induction of labor proceeded, resulting in the spontaneous vaginal delivery of a 3000 gm baby. The immediate neonatal platelet count was 301,000.

Case 9: isoimmunization. A 28-year-old woman, gravida 2, para 1, was referred for consultation because of a previous fetal death at 36 weeks in her first pregnancy. In the current pregnancy an anti-Kell titer of 1:32 was identified at 14 weeks' gestation, which subsequently rose to 1:2048 by the 19th week of gestation. In view of the findings by Rodeck et al.[8] that determinations of amniotic fluid optical density at 450 nm correlate poorly with fetal hematocrit prior to 24 weeks of gestation, the patient and her husband (Kell positive) agreed to have percutaneous umbilical blood sampling performed. An anterior placenta was traversed, and 1 ml of fetal blood was obtained with a hematocrit of 36%. The fetal anti-Kell antibody titer was 1:32, the blood type was determined to be Kell negative, and the direct Coombs test was negative. Based on these results, the patient was returned to her primary physician for continuing care, and the pregnancy progressed uneventfully.

Case 12: equivocal fetal hypoxia. A 24-year-old woman, gravida 5, para 2, abortuses 2, was admitted to the labor floor at 32 weeks of gestation in premature labor with a temperature of 38.4° C. Urine analysis revealed a urinary tract infection. Amniotic fluid was negative for bacteria by Gram stain. The patient's urinary tract infection was treated with intravenous ampicillin and terbutaline. Her temperature dropped to 37.8° C, and contractions slowed to an interval of 6 to 7 minutes. Despite discontinuation of the terbutaline, the baseline fetal heart rate remained at 180 bpm with repetitive late decelerations. These did not abate with nasal oxygen administration or with left lateral positioning. In order to gain more precise information about this potentially asphyxiated premature fetus, percutaneous umbilical blood sampling was performed at the bedside through an anterior placenta. Umbilical vein blood had a pH of 7.36, a P_{O_2} of 24, P_{CO_2} of 42, and a base deficit of −4. In view of these normal findings, the patient was managed expectantly. The fetal heart rate subsequently dropped to 150 bpm, and the late decelerations disappeared.

Thus far it has been possible to obtain a sample of fetal blood in all 13 diagnostic cases attempted, although one patient required two procedures in order to obtain an adequate sample. In no case was there evidence of fetal bleeding during or after a needle insertion. Postprocedure fetal heart rate monitoring was only undertaken in the third-trimester patients, and no abnormal patterns were noted. Although five patients were premedicated with intravenous diazepam and meperidine, no significant discomfort was experienced during the procedure. Inspection of the umbilical cords of those delivering soon after percutaneous umbilical blood sampling (Cases 7, 8, and 13) failed to show any evidence of trauma.

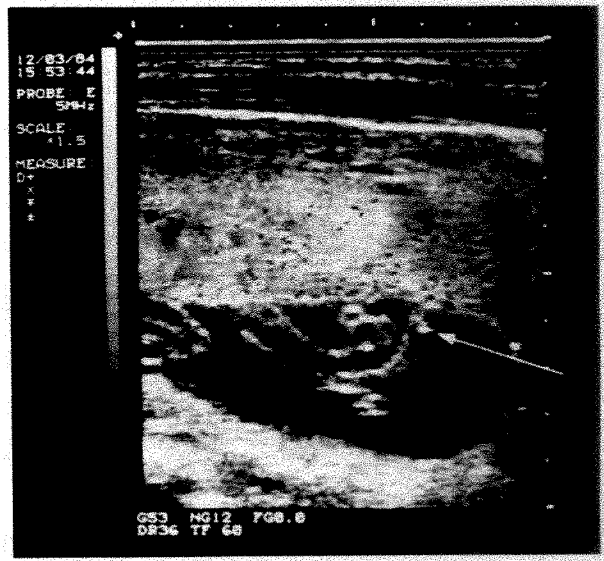

Fig. 4. Actual ultrasound scan through long axis of umbilical cord insertion site. *Arrow* points to needle tip.

Comment

This report demonstrates that it is possible to obtain fetal blood consistently by percutaneous umbilical blood sampling in the second and third trimester of pregnancy. The procedure is easier to perform in the third trimester because the umbilical cord is larger. For example, the mean diameter of the umbilical vein increases linearly from 6.5 ± 0.35 mm (1 SD) at 20 weeks to 10.1 ± 0.5 mm (1 SD) at 30 weeks, after which the diameter plateaus to a mean of 11.5 ± 0.6 mm (1 SD) at 40 weeks.[9] The further the target is from the maternal skin, the more difficult it is for the operator to guide the needle into the umbilical cord. A small adjustment in the angle at skin level has a major effect on the ultimate position of the needle tip if the selected sampling site is 8 to 9 cm away. Therefore, posterior placentas are inherently more difficult to approach than anterior placentas (as evidenced by the larger number of needle insertions required in the cases with a posterior placenta).

Ultrasound studies give the operator information in two dimensions but do not provide information in the third dimension. This deficiency has been overcome somewhat in the technique described above by attempting to view the umbilical cord in cross section during

Table I. Second- and third-trimester prenatal diagnostic cases

Case No.	*Indication*	*Gestational week*	*Location*	*No. of insertions*	*Test performed*
1	Trisomy 20 on amniotic fluid ?	23	Fundal	2	Normal karyotype
2	Imbalanced translocation in amniotic fluid cells ? 46, XY, −14 and +(14q; 14q)	22	Anterior; velamentous insertion of cord	2	Normal karyotype
3	Fetal hemophilia A?	18	Anterior	1	Factor VIII coagulant antigens, factor VIII clotting activity, all normal
4	Fetal hemophilia A?	19	Posterior	4	Factor VIII coagulant antigens, factor VIII clotting activity, all normal
5	Fetal hemophilia A?	18	Fundal	5 2	1st day (unsuccessful), 2nd day, factor VIII; coagulant antigens, factor VIII clotting activity, all normal
6	Confirmation of trisomy 21 by amniotic fluid (parents' desire for further testing)	21	Posterior	4	Karyotype; trisomy 21 confirmed
7	Idiopathic thrombocytopenic purpura	38.5	Anterior	1	Platelet count 300,000
8	Idiopathic thrombocytopenic purpura	40	Anterior	2	Platelet count 210,000
9	High anti-Kell titer	19	Anterior	1	Kell typing, direct Coombs (negative), hematocrit
10	Kell sensitization, hydrop fetalis	28	Fundal	1	Hematocrit 22 Kell positive
11	Oligohydramnios, intrauterine growth retardation, possible chromosome anomalies	33	Posterior	1	Normal karyotype
12	Possible fetal distress in patient in premature labor with fever of unknown origin	33	Anterior	2	pH, Po$_2$, Pco$_2$, base deficit
13	Possible fetal distress in hypertensive patient in early labor with undilated cervix	35	Anterior lateral	1	pH, Po$_2$, Pco$_2$, base deficit

the sampling procedure. If the needle strays on either side of the ultrasound "slice" provided, it still should enter the vessel if the echo from the needle tip is lined up appropriately. Fixed-needle aspiration adaptors have been designed to overcome the deficiencies of "free hand" aspiration, and these may well be of benefit in the second trimester of pregnancy. However, we have found these transducers to be cumbersome in procedures such as amniocentesis and probably unnecessary in the third trimester when sampling is technically much easier. The fact that this technique can be performed at the bedside renders this procedure extremely useful in the management of even acute clinical situations.

In some cases oligohydramnios prevents sampling from the umbilical cord at its insertion site in a posterior placenta. However, in oligohydramnios or ruptured membranes one can readily obtain blood from a free loop of cord that is trapped in a small pocket of fluid (Cases 6, 12, and 13). In Case 2 it was elected not to sample near the vilamentous cord insertion, so a segment of umbilical cord was chosen near the fetal umbilicus.

The thin 25-gauge needle is ideal for percutaneous

Quality of fetal blood	*Complications*	*Pregnancy outcome*
Mixed with amniotic fluid	None	Pregnancy continued
Pure	None	Pregnancy continued
Mixed with amniotic fluid	None	Pregnancy continued
Pure	None	Pregnancy continued
Pure	None	Pregnancy continued
Pure	None	Patient chose to continue pregnancy
Pure	None	Delivered
Pure	None	Delivered
Pure	None	Pregnancy continued
Pure	None	Intrauterine transfusion performed, pregnancy continuing
Pure	None	Patient went into labor; 48 hours later fetus died of pulmonary hypoplasia
Pure	None	Pregnancy continued
Pure		Patient underwent cesarean section for fetal distress

umbilical blood sampling because it (1) causes little discomfort; (2) makes a very small puncture site in the membranes, placenta, and umbilical cord; and (3) penetrates the umbilical cord more easily than a 22-gauge needle which we utilized earlier in preabortion cases.

Although in our experience the fetus and umbilical cord seem remarkably unaffected by the sampling procedure, more study is required to fully assess the safety of percutaneous umbilical blood sampling. There is some evidence, however, to suggest that the procedure has low risk. Daffos et al.[10] report that they have performed 400 umbilical cord punctures without accident, although in seven cases a transient fetal bradycardia was noted.[5]

The cases above demonstrate the usefulness of having direct access to the fetal circulation. For example, until recently all patients with idiopathic thrombocytopenic purpura were committed to cesarean section because of the risk of intracranial hemorrhage associated with a vaginal delivery to a fetus who might have a low platelet count. Obstetric management based on fetal scalp sampling in labor[11] has allowed vaginal delivery of some idiopathic thrombocytopenic purpura patients whose fetuses were found to have a platelet count of ≥50,000. Percutaneous umbilical blood sampling, however, offers an even better alternative because it will enable the fetus with a low platelet count to avoid the early portion of labor ordinarily required to dilate the cervix to a point where fetal scalp sampling can be undertaken.

The information provided by percutaneous umbilical blood sampling in Case 9 was especially enlightening in view of the patient's history and impressive anti-Kell antibody titer. Anti-Kell antibody can have even greater lethal potential than anti-Rh antibody, and this patient would undoubtedly have been scheduled for biweekly amniocenteses, ultrasound sessions, and a battery of fetal assessment tests. Based on the fetal blood results, the expense, inconvenience, and dangers of further extensive high-risk testing were avoided.

Although antepartum and intrapartum fetal heart rate monitoring has provided invaluable information about the hypoxic fetus, there are many occasions when heart rate patterns are worrisome or confusing. In Case 12, for example, there was a sustained fetal tachycardia combined with persistent late decelerations and decreased variability. This triad of findings ordinarily would have caused us to seriously consider cesarean section. However, armed with a normal acid base profile we were able to avoid an untimely delivery at 33 weeks.

Cases 1 to 6 illustrate the utility of percutaneous umbilical blood sampling in second-trimester prenatal diagnosis. In view of the lessened potential for morbidity and the convenience of undertaking sampling in an outpatient setting, we are now using percutaneous umbilical blood sampling as a primary procedure and fetoscopy only as a backup in prenatal diagnostic cases requiring fetal blood.

In addition to the above clinical examples, access to fetal blood offers a myriad of other diagnostic possibilities. For instance, in cases in which an anomalous fetus is suspected because of ultrasound studies, a fetal karyotype can be available in 48 to 72 hours (as in Case 11). Also, if one suspects fetal disease because of a TORCH infection, cultures and IgM levels can be obtained. It will now be feasible to monitor fetal levels of various therapeutic agents such as digoxin, procainamide, and verapamil. In addition, availability of fetal blood should stimulate investigators to look for new ways to assess fetal nutrition (in small-for-dates fetuses) and chronic hypoxia (in uteroplacental insufficiency).

Overall, this safe and simple technique of obtaining either single or repeated samples of umbilical cord blood increases the reality of the unborn baby as an accessible patient for both diagnosis and treatment.

Addendum

We have now performed percutaneous umbilical blood sampling procedures in a total of 29 patients without mishap, with the exception of one patient who had premature labor 3 weeks after the sampling procedure. All pregnancies (except four that were terminated electively on the basis of the diagnostic information obtained) are continuing uneventfully.

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Advanced maternal age: The mature gravida

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A 3-year study of women ages 35 years and older who were delivered at Women's Hospital of Long Beach from January 1, 1981, to December 31, 1983, was performed to study the risks involved with advanced maternal age. The study group included 1023 women who were 35 years and older, and they were divided into parous and nulliparous groups. A control group consisting of 5343 women aged 20 to 25 years was used for comparison. Each group was analyzed for the following parameters: pregnancy complications, labor complications, delivery factors, and neonatal outcome. The results show very few statistical differences in the factors analyzed. On the basis of this 3-year study it appears that pregnancies in women of advanced maternal age in the 1980s who are delivered in a modern tertiary care center may be of no higher risk for adverse outcome than pregnancies in younger parturients. (AM J OBSTET GYNECOL 1985;152:7-12.)

Key words: Pregnancy, advanced age

Advanced maternal age has become a topic of widespread public interest. Lay journals abound with articles on this subject. The obstetric literature has not been as abundant in addressing this concern, particularly with regard to recent studies. There is a definite increase in the number of women bearing children in their 30s and 40s. This increase is due to several factors. The first is the postwar baby boom cohort. As this cohort ages in the decade of the 1980s the total number of women of 35 to 40 years (in the United States) is projected to increase 42% and the percent of births to this age group is projected to increase 37%. Conversely there will be a 20% decrease in teenage women aged 15 to 19 years and a predicted 32% decrease in births to that age category.[1] Other factors for postponing childbearing include women's career priorities, advanced education, infertility, control over fertility, late and second marriages, and financial concerns.

The definition of advanced maternal age in the obstetric literature is variable. Most authors have designated a lower limit of 35 years[2, 3] as the definition whereas others have used 40 years[4-8] and a few have indicated that >44 years represents advanced maternal age.[9, 10] Regardless of the specific age definition, pregnancies in women of advanced maternal age are considered by many to be high risk. In the eighteenth and nineteenth century this categorization was due to concern for the mother. At present the designation of high risk refers to the fetus/neonate.

The obstetric literature is not only imprecise in its definition, it is also somewhat pejorative in its attitude toward women bearing children in their 30s and 40s. The older pregnant woman has been variously referred to as being postmature,[11] obstetrically senescent,[12] premenopausal,[12] geriatric,[13] gray, elderly,[14] dangerous,[9] and participating in childbearing in the twilight of the reproductive period.[15] This study purports to analyze the outcome of pregnancy for women of advanced maternal age in the 1980s to determine what, if any, their reproductive risks might be.

Material and methods

Women's Hospital of Long Beach is a modern tertiary care center attached to Long Beach Memorial Hospital and is located in southern metropolitan Los Angeles County. Women's Hospital performs approximately 5000 deliveries each year of which approximately 10% are maternal transports. Miller's Children's Hospital is connected to Women's Hospital and has an excellent large neonatal unit.

Patient selection. The study group consisted of all patients who were delivered at Women's Hospital of Long Beach between January 1, 1981, and December

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Table I. Pregnancy complications

	≥35 yr		*20-25 yr*	
	n	%	*n*	%
Group 1. All parous pregnant women				
No. of women	780		2517	
Diabetes	48	6.2	33	1.3*
Hypertension	48	6.2	40	1.6*
Premature labor	41	5.3	242	9.6*
Group 2. Healthy parous pregnant women				
No. of women	579		2197	
Premature labor	22	3.8	171	7.8*
Group 3. All nulliparous pregnant women				
No. of women	243		2826	
Diabetes	10	4.1	49	1.7*

There were no statistical differences in pregnancy complications for group 4 (healthy nulliparous pregnant women).
*$p < 0.05$ (χ^2).

Table II. Labor complications

	≥35 yr		*20-25 yr*	
	n	%	*n*	%
Group 1. All parous pregnant women				
No. of women	780		2517	
Late decelerations	79	10.1	188	7.5*
Group 2. Healthy parous pregnant women				
No. of women	579		2197	
Maternal fever	10	1.7	85	3.9*

There were no statistical differences in labor complications for either nulliparous group 3 or 4.
*$p < 0.05$ (χ^2).

31, 1983, and were 35 years or older. For comparison the patients who were 20 to 25 years old and were delivered during the same time period were used as the control group. The data were prospectively gathered from patients and their prenatal records at the time of admission to the labor and delivery unit. The data were entered in the computer, and the data base was analyzed by χ^2. Both the study group and the control group were further subdivided as follows: group 1, all parous pregnant women; group 2, "healthy" parous pregnant women only; group 3, all nulliparous pregnant women; group 4, "healthy" nulliparous pregnant women only. The healthy groups were defined as patients who did not have hypertension, diabetes, obesity, multiple gestation, cardiovascular disease, or incompetent cervix. Also exluded from the healthy category were patients without prenatal care and grand multiparous women.

Results

There were 1023 predominantly white pregnant women 35 years and older who were delivered during the 3-year period, which resulted in an incidence of 7.1%. During this time 0.9% of the patients were 40 years or older. The 20 to 25 year age category consisted of 5343 patients, with an incidence of 37.5%. The pregnancies and their outcomes were analyzed according to four categories: pregnancy complications, labor complications, delivery outcome, and neonatal outcome.

Pregnancy complications (Table I). The pregnancy complications compared included diabetes, cardiovascular disease, preeclampsia, chronic hypertension, obesity, urinary tract infections, hydramnios, weight gain >30 pounds or <15 pounds, multiple gestation, incompetent cervix, postdate pregnancy, premature labor, rupture of membranes of >24 hours, meconium, abruptio placentae, placenta previa, and premature rupture of membranes.

Parous pregnant women. In group 1 (all parous pregnant women) there was a statistically significant increase in the incidence of diabetes and hypertension in the study group. Moreover, premature labor was less common in the study group. This finding regarding premature labor was also true for group 2 (healthy parous pregnant women). There were no statistically significant differences for groups 1 and 2 in the other areas compared.

Nulliparous pregnant women. In group 3 (all nullipa-

Table IIIA. Delivery outcomes in groups 1 and 2

	Group 1. All parous pregnant women				Group 2. Healthy parous pregnant women			
	≥35 yr (n = 780)		20-25 yr (n = 2517)		≥35 yr (n = 579)		20-25 yr (n = 2197)	
	n	%	n	%	n	%	n	%
Vertex presentation (spontaneous)	351	45.0	1547	61.6*	285	49.2	1430	65.1*
Vertex presentation (low forceps)	83	10.6	162	6.5*	50	8.6	144	6.6*
Vertex presentation (vacuum)	56	7.2	136	5.4*	52	9.0	127	5.8*
Primary cesarean section	127	16.3	241	9.5*	64	11.1	123	5.6*
Repeat cesarean section	159	20.4	420	16.6*	126	21.8	366	16.7*
%Local anesthesia	228	29.2	944	37.6*	175	30.2	850	38.7*
Epidural anesthesia	415	53.2	1183	46.9*	314	54.2	1040	47.3*

*$p < 0.05$.

Table IIIB. Delivery outcomes in groups 3 and 4

	Group 3. All nulliparous pregnant women				Group 4. Healthy nulliparous pregnant women			
	≥35 yr (n = 243)		20-25 yr (n = 2826)		≥35 yr (n = 199)		20-25 yr (n = 2368)	
	n	%	n	%	n	%	n	%
Breech presentation	19	7.8	122	4.3*	18	9.0	101	4.3*
Vertex presentation (spontaneous)	82	33.7	1397	49.4*	62	31.2	1133	47.8*
Cesarean section	99	40.7	641	22.6*	78	39.2	511	21.6*
Failure to progress as indication for cesarean section	39	39.4	293	45.7*	30	38.5	248	48.5*
Local anesthesia	45	18.5	763	27.0*	40	20.1	680	28.7*
Epidural anesthesia	172	70.8	1814	64.2*	145	73.9	1551	65.4*

*$p < 0.05$.

rous pregnant women) there was an increased incidence of diabetes in the study group. Neither group 3 nor group 4 (healthy nulliparous pregnant women) indicated a difference in other pregnancy complications between the study group and the control group.

Labor complications (Table II). Ten categories of labor complications were compared. They included bleeding, maternal fever, fetal bradycardia, fetal tachycardia, prolonged decelerations, late decelerations, severe variable decelerations, precipitous labor, prolonged first stage of labor, and second stage of labor >2 hours.

Parous pregnant women. For group 1 (all parous pregnant women) late deceleration patterns were more common in the study group. For the healthy parous pregnant women (group 2) in the study group there was also a nonsignificant trend toward more late deceleration patterns during labor. Interestingly there were significantly more intrapartum maternal fevers among the healthy parous pregnant women in the control group.

Nulliparous pregnant women. There were no significant differences between the study group and the control group in the categories compared under labor complications for either nulliparous group (groups 3 or 4).

Delivery outcomes (Tables IIIA and IIIB). The areas compared were delivery presentation (vertex—occipito-anterior, vertex—occipito-posterior, breech, and transverse lie), vaginal delivery (vertex—spontaneous, vertex—low forceps, vertex—vacuum extraction, and vaginal breech), and cesarean delivery (primary or repeat).

Also analyzed were the indications for primary cesarean delivery: antepartum fetal distress, intrapartum

Table IV. Neonatal outcomes

	≥35 yr		20-25 yr	
	n	%	*n*	%
Group 1. All parous pregnant women				
No. of women	780		2517	
Birth weight >4000 gm	126	16.2	273	10.8*
Birth weight 1501-2500 gm	54	6.5	251	9.9*
Neonatal intensive care unit admissions	90	11.5	375	14.8*
Group 2. Healthy nulliparous pregnant women				
No. of women	579		2197	
Birth weight >4000 gm	81	14.0	233	10.6*
1-min Apgar score <4	34	5.9	75	3.4*
Congenital anomalies	12	2.1	18	0.8*

There were no statistical differences in neonatal outcome parameters for nulliparous gravidas (group 3, all nulliparous pregnant women, and group 4, healthy nulliparous pregnant women).

*$p < 0.05$.

fetal distress, breech/abnormal presentation, and failure to progress. Anesthesia choices were also compared: none, local, epidural, spinal, or general.

Parous pregnant women. Although there were no differences in presentation at time of delivery in group 1 (all parous pregnant women), there were significant differences in route of delivery (Table IIIA). More women in the control group had spontaneous vaginal deliveries, whereas more women in the study group had operative deliveries. The operative deliveries included the use of either low forceps, vacuum extractors, or cesarean sections. There were more of both primary and repeat cesarean births for the older women. There was, however, no statistically significant difference in the indications for primary cesareans. Epidural anesthesia for older women was used more frequently and local anesthesia less frequently. Results in group 2 (healthy parous pregnant women) also demonstrated an increse in operative deliveries for older women. Vacuum extractors were used more often, and there were more primary and repeat cesarean births. Breech presentation as an indication for primary cesarean deliveries was significantly increased for the older study group. The difference in anesthesia choices persisted in this healthy parous group. Older women received more epidural and less local anesthesia.

Nulliparous pregnant women. For group 3 (all nulliparous pregnant women) there were more breech presentations in the study group (Table IIIB). There were also fewer spontaneous vaginal deliveries and more primary cesarean sections. A lower percentage of older women had the diagnosis of failure to progress as an indication for primary cesarean delivery. The difference in anesthesia choices was the same as for the parous women. Epidural anesthesia was used more often and local anesthesia less often for older women than for the younger control group.

Healthy nulliparous pregnant women (group 4) in the study group had more forceps deliveries, more primary cesarean sections, more epidural anesthesia, and less local anesthesia than those in the healthy younger control group.

Neonatal outcomes (Table IV). Seven categories of neonatal outcomes were compared. They included stillbirth, neonatal death, admissions to the neonatal intensive care unit, congenital anomalies, 1-minute Apgar scores <4, 5-minute Apgar scores <7, and the following birth weight categories: <500 gm, 501 to 1500 gm, 1501 to 2500 gm, 2501 to 4000 gm, and >4000 gm.

Parous pregnant women. Both parous groups 1 and 2 demonstrated an increased incidence of macrosomic babies among the older patients. In group 1 (all parous pregnant women) there were also fewer babies in the 1501 to 2500 gm weight category, and fewer neonatal intensive care unit admissions than for the babies of the younger parous pregnant women. For group 2 (healthy parous pregnant women) 1-minute Apgar scores <4 and congenital anomalies were more common among the neonates of older women. There were no statistical differences in any of the other neonatal outcome categores for either parous group.

Nulliparous pregnant women. There were no statistical differences for either of the nulliparous study groups as compared to their younger controls with respect to neonatal outcome.

Comment

Neonates. Many studies have contended that pregnancies in women 35 years and older are at high risk. Increased perinatal mortality has been a major concern.[2-4, 8, 9] Most of these studies have not taken into account the effects of the systemic diseases of aging such as hypertension and diabetes. These disease processes appear to be related to increased perinatal morbidity and mortality regardless of maternal age. Grimes[3] demonstrated an increased perinatal mortality in pregnancies of older black women. This increase disappeared when hypertensive patients were excluded. Stein's study[2] excluded women with hypertension, diabetes, obesity, and thrombophlebitis. There was no increased perinatal mortality in the offspring of these healthy older mothers. The study at Women's Hospital of Long Beach did not show an increase in the stillbirth or neonatal death rate for neonates of older women. Even in the categories that showed an increased incidence of hypertension and diabetes, no difference in perinatal mortality was shown as compared to infants of younger mothers. This may speak to the effectiveness of modern prenatal and intrapartum care in a tertiary perinatal center in the 1980s. Is, however, perinatal mortality a sufficiently sensitive end point?

Outcome factors in surviving neonates analyzed in this study included prematurity, neonatal intensive care unit admissions, Apgar scores, congenital anomalies, and specific birth weight categories. The high incidence of premature labor in each of the groups is a reflection of the rate of maternal transports to this tertiary perinatal center. For the parous groups the incidence of premature labor was significantly lower in the older category than in the younger group. A study done in Norway from 1967 to 1976 also showed a decrease in preterm labor for older parous women as compared to younger parous women.[16] Corresponding to the decreased prematurity rate in the neonates of older women there was a decrease in NICU admission for those neonates. For nulliparous mothers there was no age related difference in preterm labor or NICU admissions for the neonates. The obstetrical literature is inconsistent in regards to the incidence of premature labor for nulliparous pregnant women. Waters[17] demonstrated an increase for the older nullipara woman whereas Kessler[18] did not.

Apgar scores, congenital anomalies, and birth weight categories showed some age-related differences. There was an increased incidence of low 1-minute Apgar scores and congenital anomalies in the infants of the older healthy pregnant women. Despite the lower 1-minute Apgar scores there was no increase in meconium or cesarean births for fetal distress in this group. There was an increase in macrosomic babies for the older parous pregnant women. This finding persisted even after excluding the diabetic mothers. The obstetric literature supports the finding of an increase in babies over 4000 gm in the older parous pregnant women.[3, 7, 9, 19]

Labor and delivery. Stanton's early work[9] demonstrated an increase in prolonged labor among older pregnant women. Friedman[14] showed an increse in prolonged second stage with advancing age. Many subsequent studies including the present one in Long Beach did not show an increase in prolonged labor.[2, 4, 6-8, 13]

The overwhelming majority of studies in the obstetric literature describe a significantly higher rate of cesarean births in older women.[2-9, 17-23] In this present study there was also an increased utilization of cesarean births for the older age group. It is unclear why this is so. No one specific indication for cesarean birth showed an increase in the pregnancies of women over 34 years. It may be that the increase in cesarean births for the older women is a self-fulfilling prophesy. Because the pregnancies have been considered to be at high risk, the physicians may use a lower threshold for terminating the pregnancy or the labor process.

In comparing delivery outcomes there was an increase in other methods of operative deliveries for the older study groups. At Women's Hospital of Long Beach there is a high utilization of epidural anesthesia. Pregnant women of advanced maternal age chose epidural anesthesia significantly more often than the younger parturients. This may be a contributing factor to the higher rate of forceps and vacuum deliveries for the older age group.

Elderly primigravida. The nulliparous woman of advanced maternal age deserves special comment. The designation "elderly primigravida" is used extensively in the obstetric literature and by health care providers. The term was defined in 1958 by the Council of International Federation of Obstetrics as "one aged 35 or more at the first delivery." The word elderly is a curious one to use in describing a woman in her late 30s. Elderly is defined in Webster's dictionary as "somewhat old, advanced beyond middle age: bordering on old age." Few men or women in their 30s find this description germane. Historically there may have been a place for that term when women began their childbearing in their teens and often did not live past their 40s. However, there is a current trend to postpone childbearing, and the present age span for women is well into the 70s. Therefore the label of "elderly primigravida" is obsolete and, in fact, offensive. A better choice of terms would be "mature primigravida." Mature is defined as "having completed natural growth and development, having attained a final or desired state, condition of full development."[24] When they are given good prenatal and intrapartum care and when signs of hypertension and diabetes are monitored, the risks to healthy women 35 years and older in the 1980s may be no more than the risks to the younger parturients. Perhaps the time has come to eradicate the offensive labels of elderly, dangerous, or postmature and consider these women as mature—the mature gravida.

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Palliative exenteration—What, when, and why?

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Between 1955 and 1981, 323 pelvic exenterations were performed at the Mayo Clinic. Fifty-nine (18%) were considered retrospectively to be palliative because of pelvic or aortic nodal metastasis, pelvic peritoneal involvement, pelvic wall involvement, bone involvement, or, in two cases, distant metastasis. The survivals were 47% at 2 years and 17% at 5 years. When metastatic nodal disease was found after irradiated pelvic recurrence, the 2- and 5-year survivals were 46% and 23%, respectively. Although exenteration procedures are designed to be curative, the palliative benefits obtained in this group of patients appear to be worthwhile and comparable to those achieved in advanced epithelial ovarian carcinoma for which aggressive surgical management is now strongly advocated. (AM J OBSTET GYNECOL 1985;152:12-16.)

Key words: Exenteration, survival

It has been a general opinion that pelvic exenteration should be advised and accomplished only when clinical evidence suggests potential curability. Exenteration has been considered inadvisable by some when optimal curability is diminished by the presence of nodal metastasis or by advanced pelvic spread, such as pelvic peritoneal involvement, extension into levator fascia, or extension into pelvic bone.

At times, in an effort to determine operability, the dissection may proceed beyond the point of safe return before a nonresectable area of malignancy is discovered; an unintentional palliative exenteration is the result. In rare cases, an intentional palliative exenteration has been accomplished in patients with unmanageable, malignant, postirradiation fistulas. Although early death of these patients was expected after palliative operations, a number of them have enjoyed

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sustained periods of good health. These observations, coupled with the currently advocated radical cytoreductive surgical (palliative) procedures for ovarian malignancy, prompted a retrospective review of patients considered to have had palliative pelvic exenterations at the Mayo Clinic.

Material

On retrospective review of the 323 patients who underwent pelvic exenteration at the Mayo Clinic between 1955 and 1981, 59 (18%) of the operations were considered to have been palliative because of pelvic or aortic nodal involvement, pelvic peritoneal involvement, pelvic wall involvement, or direct extension of cancer into bone. Two of these patients were considered to have had distant metastasis: to an inguinal lymph node in one and to the lung in the second (lung lesion presumed to be metastatic but with no biopsy performed).

The mean age of this group of patients was 51 years (range, 16 to 81 years).

The primary malignancy was cancer of the cervix in 37 patients, of the vagina in 10 patients, of the endometrium in four patients, of the vulva in one patient, of the rectum in two patients, of the bladder in one patient, and of the urethra in three patients and malignant melanoma in one patient.

There were three major categories of palliative exenterations: for recurrent disease after pelvic irradiation, for recurrent disease after surgical treatment alone, and as the primary therapy (Table I). Total exenteration had been performed in 34 patients, anterior exenteration in 24, and posterior exenteration in one.

Pelvic nodal involvement in the irradiated pelvis was the most frequent adverse finding and occurred in 26 patients. In 13 of these patients, only one node was involved; in seven, two nodes were involved; and in six patients, more than two nodes were involved or involvement was bilateral. Table II shows the sites of spread in each of the three categories. Pelvic nodes were involved in 35 patients, aortic nodes in three, pelvic peritoneum in nine, pelvic wall in five, and bone in five. In one patient, an inguinal node contained cancer and in one patient, an unsampled lung lesion was considered to be cancerous.

Results

The mean postoperative hospital stay was 22 days (range, 1 to 60 days), including three patients who died in the postoperative period. Hospital stay was <20 days for 49% of patients and <1 month for 78%.

Three patients had fatal postoperative complications; however, four patients (7%) died within 3 months after operation, at 1, 38, 51, and 86 days (Table III).

Thirty-five patients (59%) received no postoperative treatment. Twenty-four patients received postoperative treatment, eight immediately after operation and 16 at the time progression of disease was detected clinically. Of the eight receiving immediate treatment, five had primary pelvic or para-aortic irradiation and three had pelvic reirradiation. Of the remaining 16, three had irradiation for extrapelvic osseous metastasis, 11 had chemotherapy, and two had progestational hormone therapy. One of these 16 patients had a partial response to megestrol acetate. The others failed to show any significant response to therapy.

The median survival for the total group of 59 patients was 19 months (mean survival, 35 months; range, 0 to 170 months). Twenty-eight patients (47%) survived longer than 2 years; 10 patients (17%) survived 5 years or more.

Forty-four patients had palliative exenteration for carcinoma recurrent after irradiation or operation. When the cancer had recurred within 2 years after initial treatment, the median survival was 20 months (mean, 30 months); when it recurred more than 2 years after initial treatment, the median survival was 38 months (mean, 48 months).

The median survival in patients with pelvic node involvement was 19 months for those who had prior pelvic radiation therapy, 28 months for those who had prior operation only, and 30 months for patients in whom exenteration was performed as primary therapy. If only one or two unilateral lymph nodes were involved

Table I. Indications for exenteration

Indication	*n*
Recurrent cancer after irradiation	42
Recurrent cancer after operation alone	2
As primary therapy for cancer of	15
Vagina	8*
Urethra	2
Cervix	1
Vulva	1
Endometrium	1
Bladder	1
Rectum	1
Total	59

*Includes one patient with melanoma of the vagina.

Table II. Reason for palliative exenteration

Site	*After irradiation*	*After operation*	*Primary therapy*
Pelvic node(s)	26	1	8
Aortic node	1	1	1
Pelvic peritoneum	6*	–	3
Pelvic wall	4	–	1
Bone	3	–	2
Lung	1	–	–
Inguinal node	1	–	–

*Includes one patient with ovarian involvement.

Table III. Patients dying within 3 months after operation

Case No.	*Age (yr)*	*Primary cancer*	*Initial treatment*	*Reason for palliation*	*Survival (days)*	*Cause of death*
1	44	Cervix	Radiation	Positive pelvic node (1)	1	Cardiogenic shock
2	58	Cervix	Radiation	Positive pelvic node (1)	38	Small bowel obstruction, sepsis
3	60	Cervix	Radiation	Positive pelvic wall	51	Pancreatitis, fistulas, sepsis
4	41	Melanoma, vagina	Primary operation	Positive pelvic nodes (3)	86	Progression of melanoma

Table IV. Individual survival (in months) after palliative exenteration, by site when other than pelvic nodes

		Survival (mo)		
Site	*No.*	*After irradiation*	*After operation*	*Primary therapy*
Aortic node	3	8	51*	66*
Pelvic peritoneum	9	4, 6, 12, 19, 40, 84	–	3, 4, 10
Pelvic wall	5	2, 45, 57, 70	–	8
Bone involved	5	19, 21, 57	–	13, 19
Distant	2			
Inguinal node		89	–	–
Lung		43	–	–

*Patients received para-aortic irradiation therapy following exenteration.

Table V. Survival of patients with extension to peritoneal surface

	Survival (mo)	
Peritoneum involved	*After irradiation*	*Primary therapy*
Bladder	12, 84	10
Bladder and ileum	40	
Ileum	6	
Sigmoid	4	3,* 4†
Ovary	19	

*Primary melanoma of vagina.
†Primary bladder cancer.

(21 patients), the median survival was 20 months (range, 0 to 170 months); if three or more nodes were involved or if bilateral involvement occurred (five patients), the median survival was 19 months (range, 15 to 40 months). Twelve patients (46%) with pelvic nodal involvement after pelvic irradiation survived more than 2 years and six (23%) survived 5 years or more.

After a primary exenterative operation, eight patients had pelvic nodal involvement. The median survival was 30 months (range, 4 to 129 months). Five patients (62.5%) survived more than 2 years; only one patient (12.5%) survived more than 5 years. One patient had postoperative pelvic irradiation; she survived 49 months.

In the patient who had pelvic nodal involvement at exenteration after postoperative recurrence, one common and one external iliac node were involved. No postoperative therapy was given, and the patient survived 28 months.

The survival, in months, for each patient who had other sites of involvement is shown in Table IV.

The patient with inguinal node involvement was 36 years old, and she had recurrent squamous carcinoma 26 months after pelvic irradiation for Stage III carcinoma of the cervix. The symphysis and right pubic ramus were resected at total exenteration. Periosteum was involved, but no osseous metastases were noted. Multiple external iliac nodes were also involved. She is alive 89 months after exenteration.

In the patient with a lung metastasis, the lesion developed 10 months after irradiation and operation for Stage I cancer of the endometrium had been completed. Progestin therapy induced a prolonged partial response. A pelvic mass was noted 109 months after initial treatment and, when the patient was 52 years old, total exenteration was performed to remove all pelvic cancer. She continues on a regimen of megestrol acetate and is alive at 43 months after operation.

In no patient surviving more than 8 months was gross disease left behind at the time of exenteration. The survival of patients with pelvic peritoneal involvement is shown in Table V.

Table VI. Summary of patients alive at analysis

Age (yr)	*Primary site*	*Initial treatment*	*Time from initial diagnosis to recurrence (mo)*	*Reason considered palliative*	*Survival (mo)*
51	Vagina	Primary operation	–	Positive aortic node	66*
81	Vulva	Primary operation	–	Positive pelvic node	22
50	Vagina	Primary operation	–	Positive pelvic node	49*
45	Urethra	Primary operation	–	Positive pelvic node	129
55	Cervix	Irradiation	199	Pelvic wall	57
48	Cervix	Irradiation	27	Pelvic wall	70
48	Cervix	Irradiation	4	Bone	57
42	Endometrium	Irradiation	109	Chest metastasis	43†
36	Cervix	Irradiation	26	Inguinal node	89
37	Cervix	Irradiation	27	Positive pelvic node	98
64	Vagina	Irradiation	9	Positive pelvic node	119
48	Cervix	Irradiation	6	Positive pelvic node	123

*Received postoperative irradiation.

†Alive with stable chest metastasis.

Twelve patients were living at the time of this analysis. Four of these had had primary operation and eight had prior pelvic irradiation (Table VI).

Comment

When Brunschwieg first reported his results after exenterative operations 4 decades ago, the mortality and complication rate associated with this procedure were so high that, since that time, a major goal of gynecologic surgeons has been to improve operative survival and the chance for cure. The first objective of a gynecologic surgeon is proper selection of patients for exenterative operations. Proper selection, by itself, has significantly reduced the mortality and morbidity associated with this radical gynecologic procedure. In addition, numerous surgical[1, 2] advances, most notably Bricker's method of urinary diversion and the use of omentum in the management of the pelvic floor,[3] have led to decreases in mortality and complication rates and, henceforth, to improved survival and quality of life for many patients suffering from recurrent or advanced pelvic cancer.[4]

Barber and Jones[5] reported a series of 263 patients who underwent exenteration for recurrent cancer of the cervix after pelvic irradiation. Pelvic lymph nodes were negative in 166 patients, and 29 of these (17.4%) survived for 5 years. In the other 97 patients, lymph node involvement was noted and only five of them (5.2%) survived 5 years. Twenty-one of the patients (21.6%) with lymph node involvement died in the postoperative period. From this experience, it was concluded that, because the survival was so poor, the complication rate so high, and, in the vast majority of patients, the survival so brief and difficult, pelvic exenteration was contraindicated in patients with involved pelvic lymph nodes complicating recurrent cancer.

Table VII. Survival in patients with pelvic nodal metastases complicating pelvic recurrence after irradiation

	Survival			
	At 2 years		*At 5 years*	
	No.	*%*	*No.*	*%*
Barber and Jones[5] (1971)	–	–	5/97	5
Morley et al.[7] (1971)	0/6	0	–	–
Rutledge et al.[6] (1977)	–	–	2/30	7
This report	12/26	46	6/26	23

Rutledge et al.[6] considered exposure of pelvic peritoneum to penetrating cancer or small metastatic lesions in pelvic nodes that were in a localized area to be a debatable contraindication to performing exenteration. Thirty patients with recurrent cervical or vaginal cancer had pelvic or inguinal lymph node metastases in their series and only two survived more than 5 years. Seventy-six percent died of recurrent cancer within 2 years. Morley et al.[7] also felt strongly that exenteration should not be undertaken as a palliative procedure and reported a series of 21 patients including six with lymph node involvement; there were no survivors at 2 years.

The results in our series differ markedly from those cited above, most notably our results with exenteration for postirradiation recurrence when metastatic pelvic nodal disease is found. We obtained a 46% 2-year survival and a 23% 5-year survival (Table VII). The reasons for this disparity are not clear.

The observed lack of serious morbidity, the short hospital stay, and the length of survival in our group of 59 patients are impressive. They are similar to the results in Stage III epithelial ovarian carcinoma, for which extensive, radical, debulking operations are encouraged—including bowel resection or, at times, colostomy—to reduce tumor size to 1 to 2 cm: 49% 2-year survival and 15% 5-year survival as reported by Smith and Day,[8] except following exenteration only 40% received postoperative chemotherapy, radiotherapy, or hormone therapy.

In conclusion, the duration of hospitalization, the morbidity, and the mortality associated with exenterative surgical procedures are actually significantly lower now than those noted in this retrospective review (1955 to 1981). In view of this and the duration of survivals reported here, it appears reasonable for the experienced pelvic surgeon to proceed with a palliative exenteration whenever good clearance of the malignancy can be achieved, despite the presence of a single or multiple lymph node metastases, despite direct extension of tumor to involve peritoneum of the bowel (sigmoid, ileum) or bladder, and despite resectable tumor extension into or through fascia covering the levator muscles. Obviously, considered surgical judgment and discretion must be exercised in the selection of those patients who can tolerate the palliative operative procedures without excessive morbidity, who are capable of adjusting promptly to the postoperative physiologic alterations, and who can enjoy in comfort the additional survival potentially provided by operation.

The mere mention that benefit could be achieved in selected cases through the use of a palliative exenteration has met with vigorous opposition in the past. The present data may help to quell that disagreement.

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The importance of primary diagnosis in perinatal death

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In a referral perinatal center a detailed study was made of all the perinatal deaths that occurred during 1 year; they were analyzed according to primary diagnoses on the basis of a classification by R. L. Naeye which included the placenta. This method points to the areas in which special efforts at prevention should be made, and it should become a reliable basis for comparison. (AM J OBSTET GYNECOL 1985;152:17-23.)

Key words: Perinatal death, primary diagnosis

One of the most obvious tenets in medicine is that a diagnosis is necessary before either treatment or prevention can be implemented. The main obstacle in the field of perinatal medicine has been the complicated physiopathologic processes encountered in the two individuals involved, as well as in the special fetal organ, the placenta.

Since perinatal death is the last of a chain of events, which begin at the moment of fertilization or before, different systems of analysis can suggest a number of equally valid diagnoses. Most studies of mortality have emphasized diagnoses of the newborn,[1, 2] another emphasized those of the mother[3] and some emphasized a combination of these[4, 5]; very few have included the placenta.[6] The possibility of correlating such studies has therefore been remote. Most of the pathologic conditions leading eventually to death can be found in the obstetric history and the placenta. These tend to be omitted from studies based on the newborn infant; thus these studies can reveal areas in which improved neonatal care may reduce mortality but cannot deal with the principal problems of the prevention of prematurity and fetal death. This field of medicine is different from others in that the cause of death is not best determined by the autopsy, which frequently does no more than demonstrate "how" the fetus died and not "why." However, the procedure may sometimes be essential and should always be carried out to complete the final details.

It was therefore an important concept which Naeye introduced, that is, a classification of perinatal deaths based on initial or primary diagnosis leading to the death of the fetus or newborn infant, without preference to mother, fetus, or placenta and without clinical or anatomic bias.[6] This necessitated adequate clinical information, and it also required that autopsies and placental examinations be carried out in a high percentage of the cases. Following this procedure 80% of the deaths were classified into specific diagnostic categories; in the case of those without diagnosis, the placentas of one third were not available for examination. The diagnoses were useful, since they were precise and avoided general terms such as "anoxia" and "prematurity." In this way anatomic complications of prematurity, such as hyaline membrane disease, intraventricular hemorrhage, and immaturity were replaced with diagnoses of amniotic fluid infection, premature placental separation, premature ruptured membranes, cervical incompetence, and hydramnios. The term anoxia was also eliminated and replaced by diagnoses of placental growth retardation, premature placental separation, cord compression, cord knots, and placental infarcts.

The present study was carried out in a single Institution and was based on careful obstetric and pediatric records, with examination of all placentas and with a high percentage of autopsies. The purpose of the study was to evaluate this form of diagnosis in the prevention of perinatal pathologic conditions in a group of high-risk patients; it also attempted to prove the validity of this method of tabulating the "causes" of perinatal death and thereby to provide a means of making institutional, national, and international comparisons.

Material and methods

During 1982 every infant who died in the National Institute of Perinatology during Perinatal Period II[7] was examined post mortem either by means of an autopsy if permission was given or by external examination only with the use of weights and measures. An examination was made of the placentas of every infant delivered in the Institute. In a weekly session of clinicians and pathologists the clinical history of mother and infant as well as the anatomic findings were evaluated, the principal primary diagnoses as well as autopsy diagnoses

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Table I. Perinatal deaths and the autopsy diagnoses

*Autopsy diagnosis**	*No. of cases*	%
Macerated stillbirth	25	28
Failure of lung expansion	16	18
Intraventricular hemorrhage	11	12
Malformations†	10	11
Recent stillbirth	10	11
Hyaline membrane disease	5	6
Meconium aspiration	3	3
Bronchopulmonary dysplasia	2	2
Infection (pneumonia, enterocolitis)	2	2
Neuronal damage	2	2
Other	4	5
Total with autopsy	89	

*In cases with more than one important anatomic diagnosis, preference was given to infection, meconium aspiration, and intraventricular hemorrhage in that order.

†Five died with pulmonary hypoplasia caused by urinary tract obstruction or prolonged ruptured membranes.

Table II. Perinatal deaths in 1982 and the primary diagnoses

Primary diagnosis	*No. of cases*	%	*Naeye's[1] series (%)*
Amniotic fluid infection	14	13.3	16.7
Placental growth retardation	14	13.3	2.3
Malformations	13	12.4	9.3
Premature placental separation	9	8.6	10.5
Premature rupture of membranes	6	5.7	10.1
Cord compression	3	2.9	3.4
Cord pathology	3	1.9	1.1
Trauma	3	2.9	1.7
Cervical incompetence	3	2.9	0.7
Erythroblastosis fetalis	2	1.9	4.2
Hydramnios*	2	1.9	0.7
Ruptured uterus	1	1	0.5
Infection	1	1	1.4
Placental infarct	1	1	6.1
Other disorder†	10	9.5	8.5
Unknown cause	20	19	20.3
Total	105		

*Twins, monozygotes.

†Not included in Naeye's work.

Table III. Duration of pregnancy in cases of perinatal deaths according to the groups of primary diagnoses

	Duration of pregnancy					
	<28 weeks		*28-37 weeks*		*>37 weeks*	
Primary diagnosis	*n*	%	*n*	%	*n*	%
Amniotic fluid infection	10	71	4	29	0	0
Placental growth retardation	2	14	8	57	4	29
Malformations	2	15	7	54	4	31
Premature placental separation	2	29	5	71	0	0
Premature rupture of membranes	2	33	4	67	0	0
Intrauterine device	3	75	1	25	0	0
Unknown cause	3	15	6	30	11	55
All diagnoses	31	30	49	47	25	24

Table IV. Perinatal period in which deaths occurred according to groups of primary diagnoses

	Intrauterine period		*Neonatal period*	
Primary diagnosis	*n*	%	*n*	%
Amniotic fluid infection	1	7	13	93
Placental growth retardation	12	86	2	14
Malformations	2	15	11	85
Premature placental separation	1	14	6	86
Premature rupture of membranes	1	17	5	83
Intrauterine device	1	25	3	75
Unknown cause, mature fetus	7	64	4	36
Unknown cause, preterm	3	33	6	67
All diagnoses	40	38	65	62

were elaborated separately, and the possibility of prevention was discussed. The primary diagnoses were defined according to Naeye's classification, although some changes were occasionally introduced. These primary diagnoses were as follows:

1. Amniotic fluid infection. An anatomic diagnosis of chorioamnionitis which required membranes to be intact at the onset of labor.

2. Placental growth retardation. An anatomic diagnosis in which the placenta was 40% or more below normal weight for gestational age.[8]

3. Malformations. An anatomic (or clinical) diagnosis of cases in which the anomalies were incompatible with survival. This category took precedence over all others.[5]

4. Premature placental separation. A clinical diagnosis of severe bleeding from the placental site or an anatomic diagnosis of adherent retroplacental clot. This diagnosis took precedence over the diagnosis of amniotic fluid infection.

5. Premature rupture of membranes. A clinical diagnosis of membrane rupture prior to 37 weeks' gestation, occurring before the onset of labor.

6. Cord compression. A clinical diagnosis in which there was cord prolapse or retention of the head in a breech delivery; in this group the cord was the prime factor in an obstetric emergency.

7. Cord pathology. An anatomic (or clinical) diagnosis in which cord anomalies, including tight knots, were the only possible explanations to account for a death occurring during labor. (In cases in which Wharton's jelly remains intact, it is doubtful whether intrinsic

Table V. Fetal growth and perinatal deaths according to primary diagnoses

	*Fetal growth**			
	Small for gestational age		*Not small for gestational age*	
Primary diagnosis	*n*	%	*n*	%
Amniotic fluid infection	2	14	12	86
Placental growth retardation	12	86	2	14
Malformations	8	62	5	38
Premature placental separation	1	11	8	89
Premature rupture of membranes	1	17	5	83
Intrauterine device	0	0	4	1.0
Unknown cause, mature fetus	2	22	7	78
Unknown cause, preterm	2	18	9	82
All diagnoses	34	32	71	68

*Reference 13.

Table VI. Institutional antenatal control and perinatal deaths according to primary diagnoses

Primary diagnosis	*With antenatal control*		*Without antenatal control*	
Amniotic fluid infection	3	21	11	79
Placental growth retardation	6	43	8	57
Malformations	10	77	3	23
Premature placental separation	3	33	6	67
Premature rupture of membranes	4	67	2	33
Intrauterine device	2	50	2	50
Unknown cause, mature fetus	4	36	7	64
Unknown cause, preterm	2	22	7	78
All diagnoses	49	47	56	53

Table VII. The medical possibility of prevention and perinatal deaths according to primary diagnoses

	Not preventable		*Preventable*	
Primary diagnosis	*n*	%	*n*	%
Amniotic fluid infection	13	93	1	7
Placental growth retardation	9	64	5	36
Malformations	11	85	2	15
Premature placental separation	5	57	3	43
Premature rupture of membranes	5	83	1	17
Intrauterine device	3	75	1	25
Unknown cause, mature fetus	6	55	5	45
Unknown cause, preterm	8	89	1	11
All diagnoses	69	66	36	34

cord alterations can alone be responsible for death before the onset of labor. No nuchal cord cases should be included in group 6, but they should be included in group 7 if death occurred during labor and the cord was very tightly wound around the neck.)

8. Trauma. A clinical diagnosis in which there were mechanical difficulties in extracting the fetus, which weighed over 1000 gm and which was delivered with an otherwise inexplicable degree of hypoxia.

9. Cervical incompetence. A clinical diagnosis of an open cervix in the absence of labor, in which a cerclage had been applied to prevent infertility and in which chorioamnionitis was not anatomically present.

10. Erythroblastosis fetalis. A clinical diagnosis based on rising titers of maternal Rhesus antibodies when available, or an anatomic diagnosis when there was hydrops or evidence of severe hemolytic anemia in the fetus and the mother was Rh negative.

11. Hydramnios. A clinical diagnosis of cases in which an excess of amniotic fluid initiated premature labor. Excluded were cases of malformations accompanied by hydramnios.

12. Infection. An anatomic diagnosis of cases in which there was evidence of fetal or neonatal infection as an initial cause of deterioration, excluding problems resulting from amniotic fluid infection.

13. Placental infarcts. An anatomic diagnosis of cases in which 25% or more of the placenta was affected by infarcts, excluding cases of placental growth retardation.

14. Unknown cause. Clinical and anatomic studies could not demonstrate a primary diagnosis, whether of the death itself or of the premature onset of labor.

There were two groups with three or more cases that were not included in Naeye's series: intrauterine device, in which the premature delivery was probably due to this cause and which took preference over the diagnosis of amniotic fluid infection, and antihypertensive drugs, in which the fetal-placental unit was normally grown but in which the fetus was delivered with an unexpected degree of asphyxia, probably caused by the administration before delivery of a combination of drugs used to treat maternal hypertension.

Results

The autopsy diagnoses (Table I) revealed that problems of fetal oxygenation (macerated stillbirth, recent stillbirth, meconium aspiration) were as numerous as those of neonatal hypoxia or a combination of fetal and neonatal hypoxia (failure of lung expansion, hyaline membrane disease, bronchopulmonary dysplasia, intraventricular hemorrhage, and neuronal damage).

The distribution of the primary diagnoses was similar to that of Naeye's series (Table II), with amniotic fluid infection figuring as one of the most important groups numerically. However, in our series the diagnosis of placental growth retardation represented an equally large group; a slightly larger group was that of mal-

Table VIII. Proposed areas of prevention of perinatal mortality according to primary diagnoses

Importance of antenatal care	*Means of prevention*	*Primary diagnoses*	*No. of deaths*	*%*
Antenatal and obstetric care important	Increased vigilance at term	Unknown cause mature fetus	11	10
		Cord pathology	2	2
	Early recognition of fetal growth retardation	Placental growth retardation	12	11
		Placental infarcts	1	1
	Vigilance of bleeding; previous cesarean section	Premature placental separation	4	4
	Management of breech presentation and cord prolapse in the community	Cord compression	3	3
	Supervision of surgical procedures	Trauma	3	3
	Controlled use of depressive drugs	Antihypertensive drugs	3	3
		Subtotal	39	37
Antenatal and obstetric care possibly important, especially in twin pregnancies	Control of "irritable" uterus; revision of pathologic conditions from cerclage	Amniotic fluid infection*	16	15
		Cervical incompetence*	4	4
		Unknown cause, preterm	9	9
	Conservative management	Premature ruptured membranes	6	6
		Subtotal	35	33
Antenatal care doubtfully important; emphasis shifts to community care	Screening for diabetes; improved methods of abortion; improved contraceptive control	Malformations	6	6
		Intrauterine device	4	4
	Application of RhoGAM	Erytroblastosis fetalis	2	2
	Unknown methods	Various diagnoses	19	18
		Subtotal	31	30
		TOTAL	105	100

*Includes those with a primary diagnosis of premature placental separation in addition to this diagnosis.

formations; smaller groups were those of premature rupture of membranes and placental infarcts; about one fifth in both series were placed in the group of unknown cause.

The groups in which there were more than three cases in our series were then considered in relation to gestational age (Table III), the perinatal period in which the fetus died (Table IV), intrauterine fetal growth (Table V), autopsy diagnoses, antenatal control (Table VI), and the possibilities of prevention (Table VII).

The majority of the groups were mainly related to preterm deliveries (Table III), and the amniotic fluid infection and the intrauterine device groups were more especially related to the delivery of immature infants of <28 weeks' gestation. In the unknown cause group it was observed that the preterm infants (nine cases) were most frequently live-born whereas the mature infants (11 cases) were most frequently stillborn (Table IV); they were therefore considered separately. The only group especially related to term and postterm pregnancies was the unknown cause, mature fetus group. The majority of the groups involving preterm deliveries resulted in live births, with the exception being the placental growth retardation group, in which the majority were stillbirths.

Intrauterine growth was evaluated according to the growth curves for gestational age in two hospitals in Mexico City,[9] in which the fiftieth percentile fetal weights were as follows: 1200 gm at 28 weeks, 1900 gm at 32 weeks, 3000 gm at 36 weeks, and 3200 gm at 40 weeks. Infants with a weight below the tenth percentile for the gestational age were considered to be growth retarded. Growth retardation occurred more often than not in the placental growth retardation and the malformations groups (Table V). The unknown cause, mature fetus group was nearly always associated with normal fetal growth as were the other groups of mainly premature infants.

Antenatal control was considered positive if there had been supervision of the pregnancy in the outpatient department of the Institute for at least 4 weeks prior to the delivery; 53% of the cases had not received this much antenatal care (Table VI). The preterm groups consisting of more than 60% of the cases without antenatal care were the amniotic fluid infection, the premature placental separation, and the unknown cause, preterm groups; the groups with more than 60%

of cases with antenatal care were the malformations and the premature rupture of membranes groups. In the unknown cause, mature fetus group 63% were without antenatal care in the Institute.

The possibility of prevention was considered in relation to medical responsibility in very carefully examined individual case studies. By "preventable" we mean that death was due either to necessary treatment not being given or to unnecessary measures being taken, whether within or outside the Institute, and that it was clear that without these mistakes the fetus or infant would have survived (Table VII). According to this definition, 34% were preventable. The cases of premature rupture of membranes were not considered to be preventable; all were delivered by cesarean section in order to prevent chorioamnionitis and its consequences. Their gestational age varied between 24 and 33 weeks; it is possible that those in the upper range of 28 weeks or more could have attained greater maturity in utero with conservative measures.

The groups with more than 40% of the cases considered preventable—unknown cause, mature fetus and premature placental separation—also had not generally received antenatal control in the Institute, whereas two of the groups with more than 80% of cases considered not preventable—malformations and premature rupture of membranes—had had antenatal control. However, two groups—amniotic fluid infection and unknown cause, preterm—showed that, although generally without antenatal control, they were not considered preventable by the usual medical criteria (in 93% and 89% of cases, respectively).

Comment

The list of autopsy diagnoses (Table I) does not reveal the situations that produce hypoxia, and it is therefore of little use from the point of view of prevention. In this classification of primary diagnoses of perinatal deaths 47.6% of the diagnoses were established anatomically and 34% on examination of the placenta rather than the fetus; this highlights the importance of the placental examination.

One looks to the largest groups to find preventable factors. The amniotic fluid infection group is the most important killer of immature infants as well as the cause of many late abortions. The pathogenesis is not clear, but abnormal uterine activity has been implicated,[11] and this may be increased by sexual activity, reported to be an important antecedent factor.[12] More than one fourth of our cases had had a cerclage, which has been associated with chorioamnionitis[11]; it may be that the cerclage causes the infection, or that the infection, already present when the patient arrives at the hospital, causes the cervix to dilate through the action of prostaglandins liberated from the membranes as a result of the action of bacteria.[13] It is difficult to know if prenatal control would have prevented the early labor; Naeye and Peters[14] suggest that a large number of prenatal visits diminish the mortality resulting from chorioamnionitis, even of those patients of low socioeconomic status.

In the placental growth retardation group six of 14 cases were associated with preeclampsia and there was one case of villitis. Perhaps this group is larger than the one in Naeye's series because of a higher incidence of preeclampsia and nutritional problems in Mexico compared with the United States. In this group there were six cases with nuchal cords; five of these babies were delivered between 30 and 36 weeks. This appears to be a high incidence of nuchal cords at a gestational age at which this is not normally so common as it is at term.[10] It is unlikely that cord compression was the primary cause of death in these cases, since most fetuses died before labor; it is, however, possible that the nuchal cord was a contributing factor.

Several of the infants in the placental growth retardation group died before viability, but others might have lived if they had been delivered in time. The difficulty was to recognize the almost universally occurring fetal growth retardation in this group, especially between 24 and 34 weeks, and in those patients without hypertension, who were in the majority.

The proportion of deaths due to malformations is larger than expected in a social situation with a high mortality rate. Four cases resulted from failed abortions (pulmonary hypoplasia from prolonged ruptured membranes) or inadequate contraceptive control (drug treatment for leukemia and maternal alcoholism); four cases had a family history of diabetes, which is especially common in Mexico, two having the caudal syndrome. The five anencephalic cases had maternal histories early in the pregnancy which suggested the possibility of dehydration or local interference in the implantation. General health programs and gynecologic advice prior to the pregnancies are indicated in order to reduce the unexpected prominence of this group.

In the unknown cause, mature fetus group, only two deaths occurred after 42 weeks; some had placentas that were diminished in weight but not to the extent required by Naeye for the category of growth retarded placenta. The clinical problem is that of acute fetal distress in well-grown fetuses at term, which necessitates a closer surveillance of all patients as soon as term is reached. There were three cases with a nuchal cord, two of those fetuses being macerated.

With reference to the relationship suggested here between nuchal cords and the growth retarded placenta group and unknown cause, mature fetus group, it has been observed that abnormal cord position and variable decelerations are especially liable to occur when the fetus is growth retarded or when the case is a postdates gestation[15]; mention was made of the tendency toward a smaller quantity of amniotic fluid when the fetus is growth retarded or postterm and of the consequent accentuation of cord compression.

Unexpectedly the fetuses of the unknown cause, preterm group constituted only 12.2 of all the premature births in this series of deaths. Four were from twin pregnancies. The amniotic fluid infection group and the unknown cause, preterm group could perhaps be considered as reflections of "irritable uterus," occurring principally in the first group from 20 to 28 weeks and in the second from 28 to 37 weeks.

There have been reports of a reduction in live-born low–birth weight infants for patients receiving prenatal care, especially in socially disadvantaged groups.[16] Of all the live-born preterm infants in this series, and excluding those with malformations or an intrauterine device, a total of 25 (69%) had not had antenatal care; this is a higher proportion than for the series as a whole, although the very fact of the prematurity reduced their opportunity to receive antenatal care.

The premature rupture of membranes group included three deaths in twin pregnancies; the other three deaths involved women who were 36, 37, and 40 years old. Larger numbers will reveal whether maternal age is an important association or not. In contrast with the other preterm groups, the majority had had antenatal care.

In the premature placental separation group the two immature infants had evidence of amniotic fluid infection, an association noted by Naeye[17]; the hemorrhage could have been due to abnormal uterine movements at a gestational age in which the placenta is frequently low and easily detached. Four other cases had had one or more Cesarean section deliveries previously. Two etiologies therefore seem to be important: (1) uterine "irritability" early in the third trimester and associated with chorioamnionitis and (2) previous cesarean section.

The aim of assigning initial causes to these deaths was to identify areas of action from which the greatest reduction in perinatal mortality might be expected. In Table VIII, the primary diagnoses have been arranged with this aim in view. The first major area, in which antenatal and obstetric care is considered important, includes groups with diminished antenatal care and others, such as trauma, which were considered entirely preventable. The second major area, in which antenatal care was possibly important, includes the immature and premature groups in which, despite a high incidence of lack of antenatal care, in most cases did not seem to be preventable from a medical point of view. The third major area, in which antenatal care was of doubtful importance, includes the groups in which the patients had generally sought antenatal care and which did not seem to be preventable, at least not once the patient had become pregnant.

It can be seen that the first major area is of most importance numerically and principally involves three clinical fields: the early recognition of fetal growth retardation, increased vigilance at term, and increased vigilance of bleeding in cases of previous cesarean section.

The second major group follows closely and may be diminished by increased antenatal care, especially if means to control the "irritable" uterus are found, including in cases of twin pregnancy; it may also be diminished if cerclage pathology is reduced and if more conservative management is used for premature rupture of membranes.

The third major group in which improved general health and contraception may be of importance is smaller than the other groups and perhaps more difficult to reduce immediately.

At the moment the causes in some of the areas which are most important numerically remain mysterious; this makes prevention difficult, but perhaps these groups do gradually improve anyway as organization and social conditions improve.[18] The attack has to be made on three fronts: by improving individual obstetric care, by attending to epidemiologic processes, and by doing research into certain of the more obscure causes.

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Value of a postvoid scan during adnexal sonography

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The position of the uterus and ovaries can be affected by the degree of bladder filling. A postvoid scan may bring into view ovarian pathologic conditions not previously discerned. (AM J OBSTET GYNECOL 1985;152:23-5.)

Key words: Postvoid scan, adnexal sonography

Emphasis has been placed on the bladder as an "acoustic window" for both gynecologic and obstetric ultrasonography. The value of the postvoid scan in patients with a possible diagnosis of placenta previa has been commented on.[1] In gynecology, however, the advantage of bladder emptying by the patient and subsequent scanning has not been appreciated. Although the rectum and vagina are fixed by the pelvic diaphragm, the position of the uterus and ovaries can be affected by the degree of bladder distention. Bladder filling, however, may not be symmetrical. In the first and second trimesters, dextrorotation or levorotation of the uterus may be discerned with different degrees of bladder filling. Uterine displacement by the bladder does not occur in the third trimester, because of the relatively large size attained by the uterus and its intrauterine content. The anatomic location of the ovaries within the pelvis often depends on the position of the uterus. When the uterus is anteflexed, the ovaries are either lateral or posterior; with retroflexion the ovaries are generally superior. Since bladder filling and emptying can have such a marked effect on both the non-

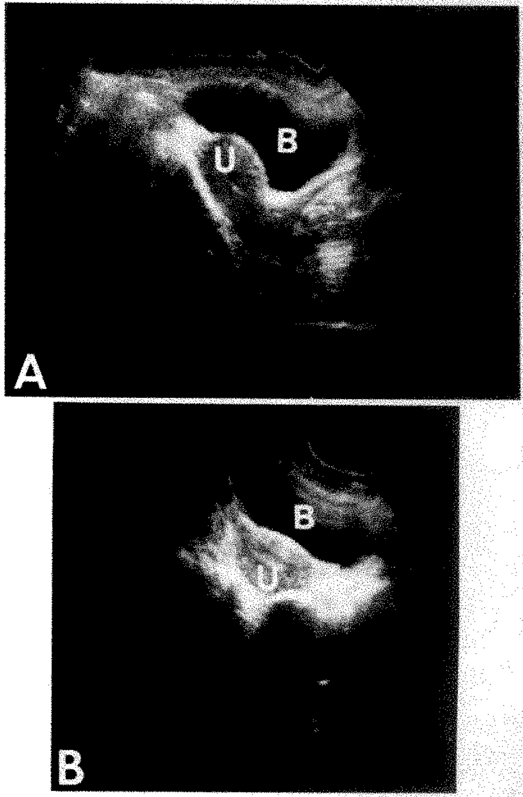

Fig. 1. (Case 1). Sonogram with bladder distention. **A,** Longitudinal scan shows anteverted, normal-sized uterus. **B,** Transverse scan. *B,* Bladder; *U,* uterus.

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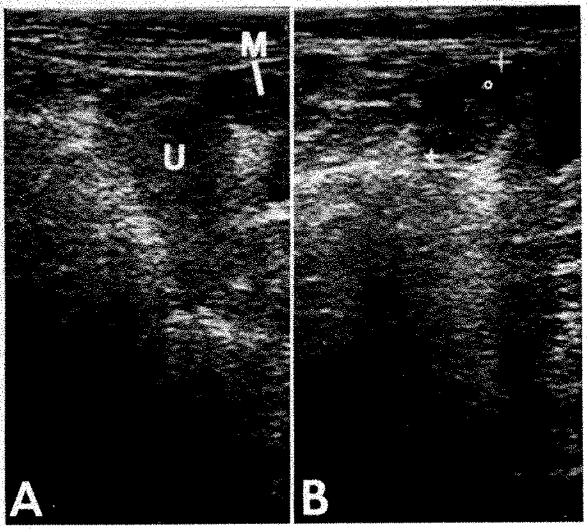

Fig. 2. (Case 1). Sonogram after bladder emptying. **A,** Longitudinal scan. *M,* Mass; *U,* uterus. **B,** Oblique scan. A 4.1 cm complex adnexal mass is indicated by *markers.*

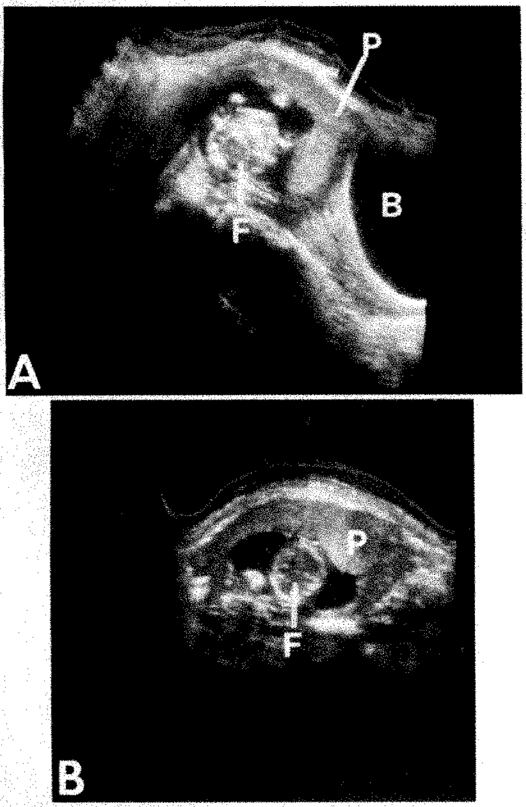

Fig. 3. (Case 2). Sonogram with bladder distention. **A,** Longitudinal scan. **B,** Transverse scan. *B,* Bladder; *F,* fetus; *P,* placenta.

gravid uterus and the gravid uterus during the first and second trimesters, ovarian position likewise will be affected. The following cases serve to illustrate this point.

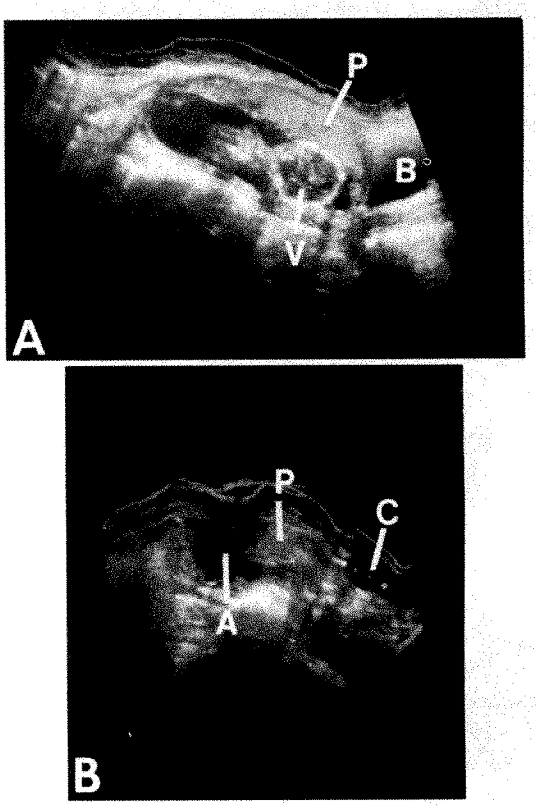

Fig. 4. (Case 2). Sonogram after partial bladder emptying. **A,** Longitudinal scan. **B,** Transverse scan at same plane as that in 3, **B.** A left adnexal cyst *(C)* is identified. *A,* Amniotic fluid; *B,* bladder; *P,* placenta; *V,* vertex.

Case reports

Case 1. A 28-year-old multigravid woman was admitted to the hospital with right lower quadrant pain and vaginal bleeding. Her past surgical history included bilateral tubal ligation 3 years before admission. With the bladder moderately full, a normal midline uterus was visualized (Fig. 1). No adnexal masses were discerned. After bladder emptying, a complex right adnexal mass (4.1 by 3.0 by 2.5 cm) came into view anterior to the uterus (Fig. 2).

Case 2. A 27-year-old woman, gravida 2, para 1, was referred to our diagnostic ultrasound unit at 18 weeks' gestation. A left ovarian cyst had been discovered on a dating scan at 12 weeks and had persisted on repeat scanning 1 month later. Initially the bladder was markedly distended, giving the impression of an anterior placenta previa (Fig. 3, **A**). No adnexal pathological conditions were visualized (Fig. 3, **B**). With partial bladder emptying, not only could the diagnosis of placenta previa be excluded (Fig. 4, **A**) but also the previously visualized left adnexal cyst came into view (Fig. 4, **B**).

Comment

Adnexal disease has been evaluated for a number of years with standard gray-scale techniques; therefore an appreciation of the sensitivity and specificity of this method has been gained.[2] The increased availability and improved resolution of real-time scanners have permitted a more rapid approach to the patient with a suspected pelvic mass. By considering the effect of bladder size on the interrelationships of pelvic structures, one can obtain a more thorough ultrasonic assessment of pelvic anatomy and disease.

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Histomorphometry of the human placenta in maternal preeclampsia

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The placentas of five mothers with severe preeclampsia who gave birth to moderately growth-retarded term infants were compared to a group of placentas collected from mothers who had uncomplicated pregnancies and normal term infants who were appropriate for gestational age. This study demonstrated that, on a quantitative histologic basis, the placentas of the preeclamptic mothers were morphologically very similar to the control placentas in terms of weight, parenchymal and cellular content, and surface areas of exchange between mother and fetus. The findings of this study support the hypothesis that, in preeclampsia not associated with severe intrauterine growth retardation, the perinatal morbidity associated with this condition is probably related more to some alterations in uteroplacental and, possibly, umbilical blood flows than to significant changes in placental structure and function. This may be due to compensatory repair mechanisms and extensive functional reserve capacities in these placentas. (AM J OBSTET GYNECOL 1985;152:25-31.)

Key words: Preeclampsia, placenta, morphologic changes, intrauterine growth retardation

Preeclampsia, still a major complication of pregnancy, jeopardizes both mother and fetus. However, many gaps still exist in our knowledge concerning the cause and pathophysiology of this disease. Furthermore, the role of the placenta in the pathogenesis of preeclampsia, and in the etiology of two of its most serious consequences during pregnancy, namely, fetal growth retardation and intrauterine fetal death, remains very obscure.

A wide variety of morphologic changes has been reported in the placentas of preeclamptic women.[1-3] To date, however, the definitive pathogenesis of these structural abnormalities, their correlation with placental function, and their relationship to perinatal loss and morbidity in these high-risk pregnancies have not been clearly established.

Since very few previous attempts have been made to characterize quantitatively the morphologic structure of these placentas,[4-6] I proposed in the present investigation, first, to define more precisely, with quantitative analyses, the morphologic changes in the functional structure of the placenta which could be attributed to maternal preeclampsia, and, second, to evaluate the possible impact of these structural changes on placental function, fetal growth and development, and the perinatal morbidity associated with this disease.

Material and methods

Ten placentas collected from Caucasian middle-class women were examined in this study. Five placentas were from primigravid women with severe preeclampsia, that is, patients in whom the systolic over diastolic blood pressure had risen 60/30 mm Hg since their last

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Table I. Maternal, fetal, and placental characteristics

Characteristic	*Control*		*Preeclampsia*		*Significance*
	Mean	*± SD*	*Mean*	*± SD*	
Mother					
Age (yr)	24.40	2.88	25.00	5.24	NS
Pregravid weight (kg)	59.18	4.11	60.91	4.23	NS
Gravid weight (kg)	70.05	7.50	76.65	24.82	NS
Height (cm)	161.78	6.66	162.21	4.41	NS
Parity (n)	1.00	–	1.00	–	–
Blood pressure					
Systolic (mm Hg)	121.00	5.48	174.00	30.50	$p < 0.01$
Diastolic (mm Hg)	77.00	4.47	114.00	13.42	$p < 0.001$
Fetus					
Gestational age (wk)	40.00	–	40.00	–	–
Birth weight (gm)	3315.00	244.69	2466.00	117.60	$p < 0.001$
Birth height (cm)	50.60	1.14	47.80	1.64	$p < 0.02$
Head circumference (cm)	34.20	0.91	32.99	0.78	NS
Placenta					
Trimmed weight (gm)	467.00	52.25	432.82	24.53	NS
Trimmed volume (cm^3)	436.60	54.34	410.60	24.43	NS
Longest diameter (cm)	20.50	1.12	19.00	1.70	NS
Transverse diameter (cm)	18.20	1.10	17.10	0.96	NS
Distance of cord implantation from margin (cm)	6.20	1.68	5.70	1.52	NS
Villous connective tissue (gm)	112.70	23.67	83.82	12.66	$p < 0.05$
Fibrin (gm)	12.87	2.24	10.89	3.80	NS
Infarcts (gm)	–	–	14.41	7.77	–
$\frac{\text{Parenchyma (gm)}}{\text{Nonparenchyma (gm)}}$	0.82	0.11	0.91	0.16	NS

SD = Standard deviation. NS = Not significant. Degrees of freedom = 8.

visit, together with proteinuria greater than 5 gm or a urine output less than 500 ml/24 hours, associated with generalized edema and signs of central nervous system hyperactivity. The patients were delivered by cesarean section at 40 weeks' gestation. None had any history of smoking or anemia during pregnancy. They gave birth to infants who were moderately growth retarded, with birth weights that ranged between 2,260 and 2,550 gm, who were below the third percentile on the Montreal intrauterine growth chart.[7] The neonatal outcome of these infants was complicated only by a moderate asphyxia in one case, and a mild respiratory distress syndrome in another. Their hematocrits, however, were all in the normal range at birth, with a mean of 51.36%. The control group of placentas was obtained from five healthy women who were similar to the study group of preeclamptic women with respect to socioeconomic status, age, weight, height, and parity. The control women had no history of anemia, high blood pressure, or smoking during pregnancy. These patients were delivered vaginally and gave birth to normal term infants who were appropriate for gestational age (range 2,995 to 3,650 gm). All infants in this study were live born and without any evidence of congenital malformation. The gestational age of the newborn infants was confirmed by an early ultrasound measurement of biparietal diameter during pregnancy, by the date of conception, and by a clinical evaluation of gestational age after birth.[8]

The placentas were histologically processed as previously described,[9] and the parenchymal and nonparenchymal components of the placental tissue were divided as shown in previous studies[10, 11]: the parenchyma included the intervillous space, the trophoblast layer (cytotrophoblast and syncytiotrophoblast), and the fetal capillaries of both peripheral and stem villi; the nonparenchyma represented the sum of decidual and chorionic plates, intercotyledonary septa, fetal vessels, connective tissue of the villi, fibrin deposits, and infarcts. In this context, the "parenchyma" was defined as that part of the placenta which contains the structures or compartments that are strictly concerned in metabolic exchanges between mother and fetus.

In the parenchymal tissue, a technique of point-counting adapted to light microscopy by means of a suitable eyepiece graticule[9] was used to measure the volume proportions of its microcomponents, such as the intervillous space and fetal capillary bed, and the numerical density of all the different types of nuclei in the villous tissue. In a similar fashion, the surface densities and areas of the villi and fetal capillaries were measured by a point-intersection counting method.[9]

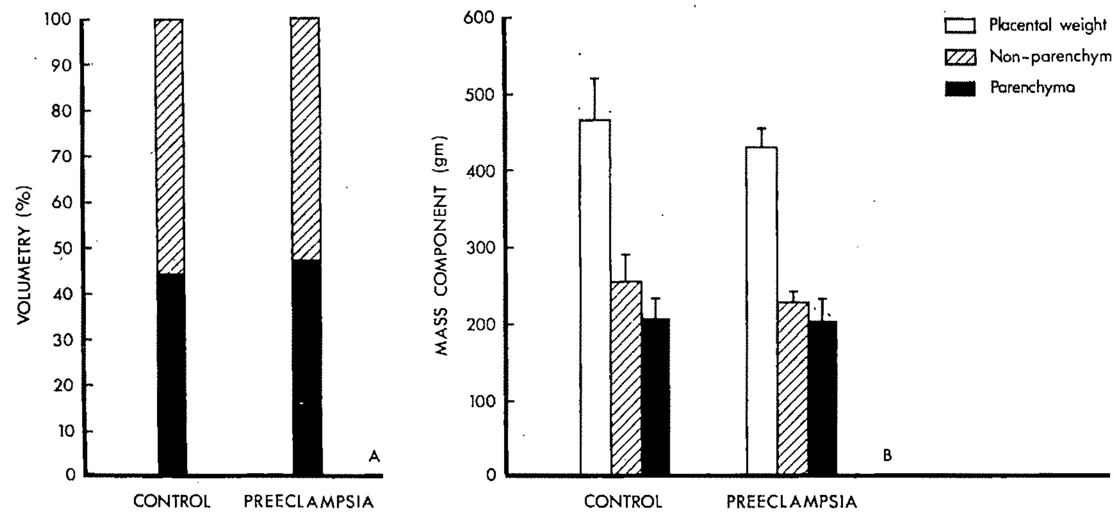

Fig. 1. Parenchymal and nonparenchymal content in relative *(A)* and absolute *(B)* values in the placentas. The placentas of the small–for–gestational age infants of the preeclamptic mothers are not significantly smaller than the control placentas, and the proportions of parenchymal and nonparenchymal tissues are similar in the two groups of placentas. (Mean ± SD.)

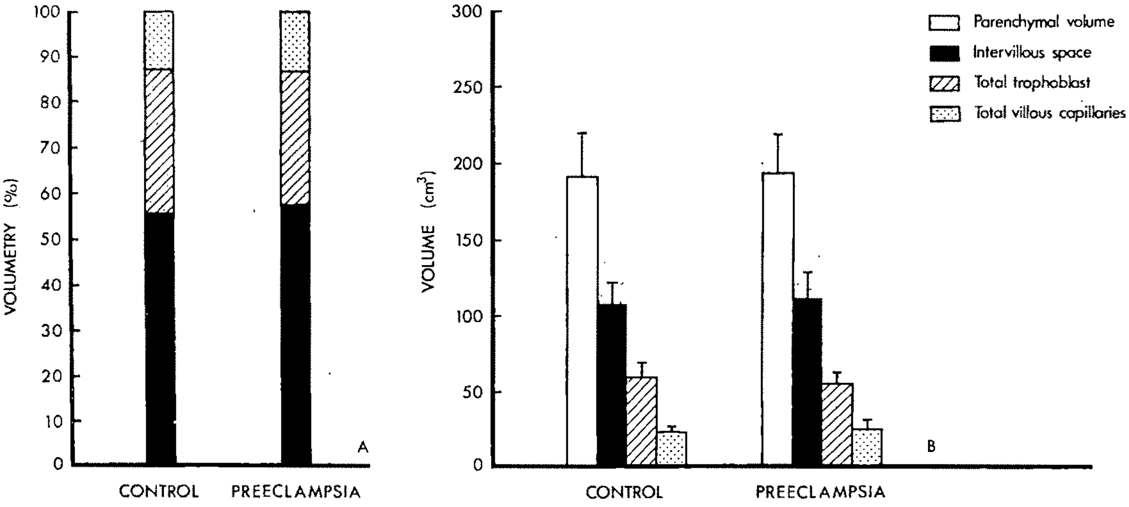

Fig. 2. Percentage distribution *(A)* and absolute volumes *(B)* for the parenchymal components in the placentas. The distributions of the parenchymal components are similar in the two groups of placentas.

The results obtained were subjected to a statistical analysis, with Student's *t* test for unpaired samples being used for this purpose.

Results

Table I displays the basic data for the mothers, the infants, and their placentas, and Figs. 1 and 2 illustrate the proportions of parenchymal and nonparenchymal tissues in the placentas. It can be seen that, although the infants of the preeclamptic mothers were significantly smaller than the control infants in terms of their mean body weight (2,466 versus 3,315 gm, $p < 0.001$) and length (47.80 versus 50.60 cm, $p < 0.02$) at birth, their mean placental weights were not significantly different (432.82 versus 467.00 gm, $p > 0.20$). In a similar fashion, no significant differences could be demonstrated in the proportions of parenchymal and nonparenchymal tissues and in the distribution of the parenchymal tissue components between the placentas of the preeclamptic mothers and the control placentas. There was significantly less villous connective tissue (83.82 versus 112.70 gm, $p < 0.05$) in the placentas of the preeclamptic mothers than in the control placentas, and although there were no infarcts in the control

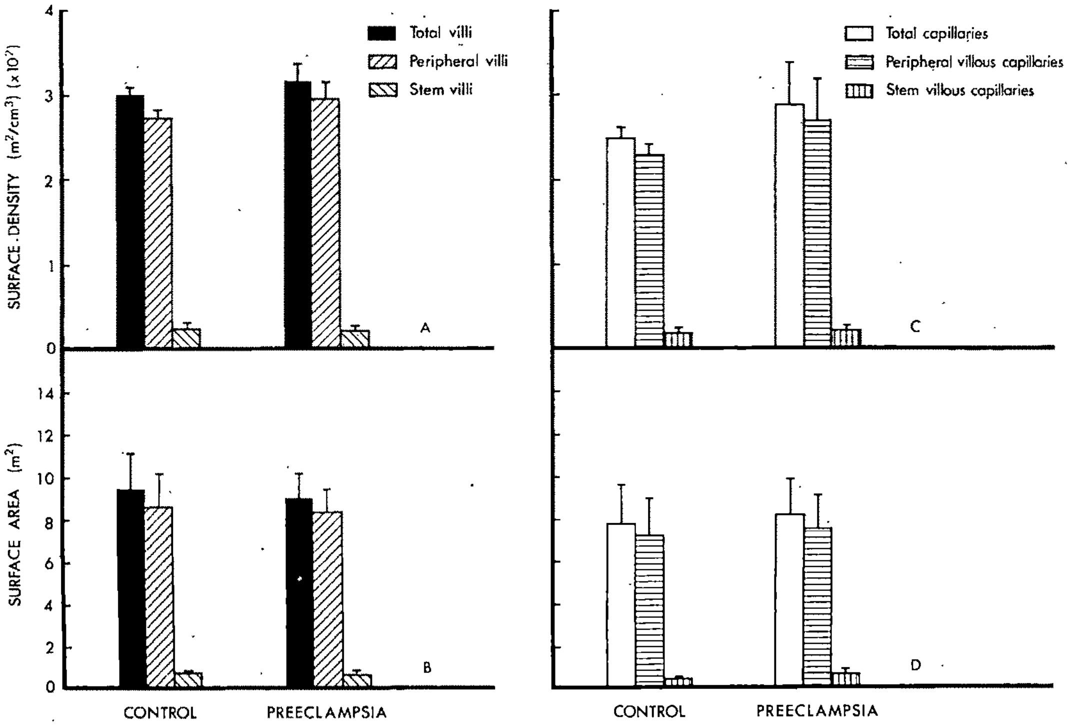

Fig. 3. Comparison between villous and capillary surface densities (*A* and *C*) and surface areas (*B* and *D*) in the two groups of placentas. There are no significant differences in these surface areas of exchange between the two groups of placentas.

group of placentas, infarcts represented no more than 1% to 5% of the placental weight in the study group.

Fig. 3 demonstrates that the villous and capillary surface densities and areas were similar in the two groups of placentas. The numerical density of all the different types of nuclei in the peripheral villous tissue is illustrated in Fig. 4. It has shown a significant decrease in the number of fibroblastic cells, and, in contrast, a significant increase in the number of Hofbauer cells in the placentas of the preeclamptic mothers compared to the control placentas. It has also shown that the syncytiotrophoblast nuclei were significantly more numerous only in relative values in the study group than in the control group (Fig. 4, *A* and *B*). It is noteworthy that no significant proliferation of the cytotrophoblast could be demonstrated in the placentas of the preeclamptic mothers.

In Table II, different parameters were compared to illustrate other aspects of the structural differences between these two groups of placentas. In the peripheral villi, the ratios of cytotrophoblastic and of syncytiotrophoblastic nuclei to villous surface area showed that they were not significantly more numerous per unit of surface area in the placentas of the preeclamptic mothers. The ratios of connective tissue and of intervillous space to total villous tissue volumes were calculated to explore the possibility that a relative reduction in the size of the villi thereby increased the intervillous space volume in the placentas of the preeclamptic mothers. The results showed a significant decrease in the connective tissue content of the villi in the placentas of the study group (0.48 versus 0.54, $p < 0.05$), and, consequently, the relative values for the intervillous space volume were significantly increased in these placentas compared to the control placentas (0.68 versus 0.56, $p < 0.02$). The ratios of capillary to villous surface areas were not statistically different at the peripheral villi level. In contrast, it showed that the mean number of syncytiovascular membranes per 100 peripheral villi was significantly higher (181.67 versus 109.93, $p < 0.001$) in the placentas of the preeclamptic mothers than in the control placentas.

Table III was prepared in order to illustrate the functional significance of these morphologic differences between the placentas of the preeclamptic mothers and the control placentas. The ratios of important parameters of placental function to fetal weight were compared, namely, placental and parenchymal weights, total trophoblast nuclei content, total villous and capillary surface areas, and intervillous space volume. It can be seen that all these ratios were significantly higher in the placentas of the study group.

Comment

The morphologic changes most commonly reported in placentas of preeclamptic women are[1-3]: increased

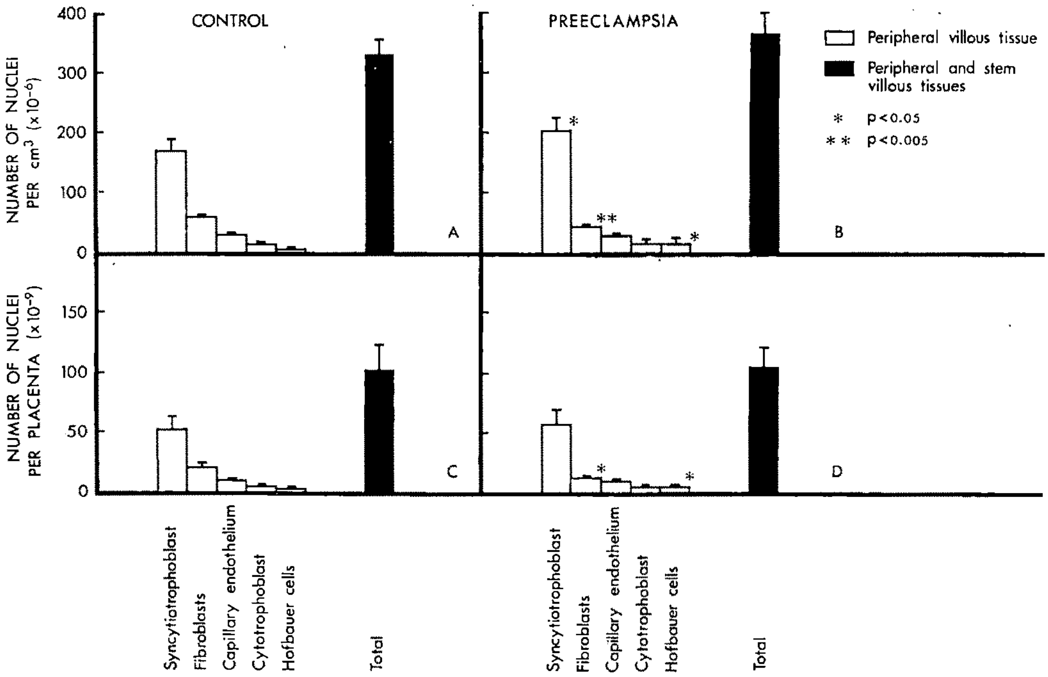

Fig. 4. Comparison between the numerical density (*A* and *B*) and the actual content per placenta (*C* and *D*) for the five different types of nuclei in the peripheral villi, and their total number in the peripheral and stem villous tissues. There is a significant increase in the number of syncytiotrophoblast nuclei in relative values and in the number of Hofbauer cells in relative and absolute values. There is a significant decrease in the number of fibroblastic nuclei.

number of true infarcts, increased syncytial knots or sprouts with focal areas of syncytial necrosis, loss and distortion of syncytial microvilli, dilatation of syncytial rough endoplasmic reticulum, decreased syncytial pinocytotic activity and reduced number of secretory droplets, thickening of the trophoblastic basement membrane, cytotrophoblastic hyperplasia, stromal fibrosis, and obliterative enlarged endothelial cells in the fetal capillaries. On a quantitative histologic basis, previous investigators have reported a significant reduction in villous and capillary surface areas,[4, 5] in the intervillous space volume,[5] and in the mass of syncytiotrophoblast.[6] The pathogenesis of these various villous lesions is still open to debate, but there is ample evidence that uteroplacental ischemia could be responsible for many of the observed placental changes, as recently reviewed by Jones and Fox.[1, 2] This hypothesis is also strengthened by the now well-confirmed demonstration of a marked reduction in uteroplacental blood flow in preeclampsia.[12]

One of the most striking features in the present study was the close morphologic similarities on a quantitative histologic basis between the placentas of the preeclamptic mothers and the control placentas, in terms of placental weight, parenchymal and cellular content, and surface areas of exchange between mother and fetus. Furthermore, in contrast to most previous qualitative[1-3] and quantitative[6] studies, no signs of significant uteroplacental ischemia could be demonstrated in the placentas of the preeclamptic mothers, in terms of cytotrophoblastic hyperplasia or syncytial degeneration.

One possible explanation for the morphologic similarities between the two groups of placentas could be that the degree of severity or the duration of the disease process was not important enough in the cases presented in this study to produce significant morphologic changes in the placentas of these preeclamptic mothers. Although it is not unusual to encounter a virtually normal[1] placenta from a woman with mild preeclampsia, and although it is still difficult to assess the time of onset of the pathologic process, the clinical severity of the disease in these patients, coupled with the intrauterine growth retardation of their infants, suggests that, theoretically, the disease was severe enough to affect the morphologic development of their placentas.

Another plausible explanation for the observations in the present study is the hypothesis put forward by Jones and Fox which suggests that compensatory mechanisms in the placenta are brought into play in preeclampsia, in an attempt to overcome the unfavorable maternal environment.[1, 2] One of these mechanisms would be, for example, the successful reparative ability of the cytotrophoblastic cells to replace the ischemically damaged syncytiotrophoblast. Another one would be

Table II. Comparison of different parameters between normal placentas and placentas of infants of preeclamptic mothers

	Control		*Preeclampsia*		
Parameter	*Mean*	*± SD*	*Mean*	*± SD*	*Significance*
Peripheral villi cytotrophoblast nuclei / Peripheral villous surface area (m^2)	4.82×10^8	0.77×10^8	5.59×10^8	1.89×10^8	NS
Peripheral villi syncytiotrophoblast nuclei / Peripheral villous surface area (m^2)	6.22×10^9	0.75×10^9	6.97×10^9	0.58×10^9	NS
Total connective tissue volume (cm^3) / Total villous tissue volume (cm^3)	0.54	0.03	0.48	0.05	$p < 0.05$
Intervillous space volume (cm^3) / Total villous tissue volume (cm^3)	0.56	0.08	0.68	0.03	$p < 0.02$
Peripheral capillary surface area (m^2) / Peripheral villous surface area (m^2)	0.84	0.04	0.91	0.13	NS
Mean No. of syncytiovascular membranes/ 100 villi	109.93	18.20	181.67	17.72	$p < 0.001$

Table III. Human placenta: Comparison of different parameters in relationship to fetal weight between normal placentas and placentas of infants of preeclamptic mothers

	Control		*Preeclampsia*		
Parameter	*Mean*	*± SD*	*Mean*	*± SD*	*Significance*
Placental weight (gm) / Fetal weight (gm)	0.141	0.015	0.176	0.014	$p < 0.01$
Parenchymal weight (gm) / Fetal weight (gm)	0.063	0.008	0.083	0.013	$p < 0.02$
Total trophoblast nuclei content / Fetal weight (gm)	61,785	9,596	99,083	8,583	$p < 0.001$
Total villous surface area (m^2) / Fetal weight (gm)	2.85×10^{-3}	0.53×10^{-3}	3.69×10^{-3}	0.51×10^{-3}	$p < 0.05$
Total capillary surface area (m^2) / Fetal weight (gm)	2.38×10^{-3}	0.50×10^{-3}	3.39×10^{-3}	0.73×10^{-3}	$p < 0.05$
Intervillous space volume (cm^3) / Fetal weight (gm)	0.032	0.005	0.045	0.007	$p < 0.01$

the formation of large syncytial projections into the intervillous space, a mechanism to increase the surface area of the syncytium that is available for transport activity. These compensatory mechanisms would function therefore with great efficiency in preeclampsia, and would explain not only the quantitative histologic similarities between these two groups of placentas, but also the fact that, in the present study (Table III), the placental/fetal weight ratio was significantly increased, as has been often reported in this condition.[1, 3]

It is worth emphasizing two aspects of this relationship between placental and fetal weight in preeclampsia: the size and morphologic structure of the placenta as determinants of (1) placental function, and (2) fetal growth and morbidity. It is important to realize that, whatever the extent of the placental lesions in preeclampsia, this pathologic condition of pregnancy is often responsible for a high rate of fetal distress and death in utero and for various degrees of intrauterine growth retardation associated with high placental/fetal weight ratios. This is in contradiction to other forms of intrauterine growth retardation in which the placenta tends to be small and the placental/fetal weight ratio is often decreased.[13] In these latter forms of intrauterine growth retardation, experimental animal studies,[14] as well as clinical observations,[15] suggest that placental size could be a major determinant of fetal growth. Furthermore, detailed morphometric studies of the placenta have demonstrated that these placentas are characterized by marked reductions in parenchymal tissues and surface areas of exchange between mother and fetus, in terms of capillary and villous surface areas and intervillous space volume.[4, 11]

In contrast, the results of the present study have shown that, in fact, the high placental/fetal weight ratio in preeclampsia was also a reflection of higher ratios for other more significant parameters of placental function to fetal weight, such as parenchymal weight, total trophoblast nuclei content, and all surface areas of exchange between mother and fetus (Table III). On a functional basis, this marked increase in parenchymal content and in surface areas of exchange per gram of fetal weight in the placentas of the growth-retarded infants, compared to the control placentas, suggests that these placentas have extensive functional reserve capacities. The transplacental transfer of respiratory gases and nutrients could also be improved by certain compensatory repair mechanisms, such as the relative increase in syncytiotrophoblast (Fig. 4, *B*), and intervillous space volume (Table II) due to the significant loss of villous connective tissue (Table I) and the reduced size of the villi, and also by the significant increase in the number of syncytiovascular membranes (Table II).

Therefore, based on these morphologic characteristics, the results of this study support the hypothesis that, in pregnancies complicated by preeclampsia not associated with severe intrauterine growth retardation, any ill effects suffered by the fetus are probably related more to some alterations in uteroplacental blood flow than to significant changes in placental structure and function. This is possibly due to efficient repair mechanisms and extensive functional reserve capacities in these placentas.

Although uteroplacental ischemia appears to be the dominant factor in the fetal morbidity associated with preeclampsia, other mechanisms may also be operative. For example, a reduction in umbilical blood flow, as a result of a lower production of prostacyclin by the fetal vasculature,[16] could play a role. Furthermore, despite the compensatory repair mechanisms, it is possible that the villous trophoblast does suffer some degree of impaired functional activity in preeclampsia. This impairment has been shown by certain ultrastructural and biochemical abnormalities in the trophoblast, such as a marked loss of syncytial microvilli and reduced enzymatic activities.[2] These observations and the findings of this report point to the need for more biochemical and physiologic investigations, as well as further cytomorphometric placental studies, in order to determine more precisely the role of the placenta in the pathogenesis of preeclampsia.

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Maternal and perinatal outcome of conservative management of severe preeclampsia in midtrimester

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Pregnancies complicated by severe preeclampsia in the second trimester are associated with a high incidence of perinatal morbidity and mortality. One way to possibly improve perinatal outcome in these pregnancies is to attempt to prolong the gestation with conservative management. Reported here the results of conservative management of 60 consecutive patients with severe preeclampsia in the second trimester (18 to 27 weeks' gestation). Although there were no maternal mortalities, the morbidity rate for the 60 patients was very high. Severe maternal complications included abruptio placentae (n = 13), eclampsia (n = 10), coagulopathy (n = 5), renal failure (n = 3), hypertensive encephalopathy (n = 2), intracerebral hemorrhage (n = 1), and ruptured hepatic hematoma (n = 1). In addition, perinatal outcome for these pregnancies was exceptionally poor, with 31 of the 60 pregnancies resulting in a stillborn infant, and 21 resulting in a neonatal death, for a total perinatal mortality rate of 87%. Thus, the results of this retrospective study do not support the use of conservative management for pregnancies complicated by severe preeclampsia in the second trimester. (AM J OBSTET GYNECOL 1985;152:32-7.)

Key words: Severe preeclampsia, midtrimester, management

Pregnancies complicated by severe preeclampsia remote from term are associated with increased rates of perinatal mortality and morbidity.[1-8] Most of the fetal-neonatal complications are related to intrauterine fetal growth retardation, prematurity, and perinatal asphyxia. In addition, such pregnancies are associated with increased rates of maternal mortality and morbidity.[1-5, 9] The optimum management of these pregnancies is controversial. Several reports in the obstetric literature have recommended conservative management in such pregnancies in an attempt to delay delivery until fetal lung maturity is achieved.[6, 7, 10] The conclusions of these reports are based predominantly upon outcomes of pregnancies between 28 and 36 weeks' gestation, wherein conservative management of variable duration was accompanied by improved neonatal outcome. More recently, in two large series of patients with eclampsia[11] and severe preeclampsia,[1] neonatal survival rates of approximately 95% were reported for gestations beyond 28 weeks. In both of these studies, aggressive management, including prompt delivery, was recommended for all severely preeclamptic patients with gestations beyond 28 weeks.

There are few published case reports[2-7, 12, 13] of conservative management of severe preeclampsia in the second trimester. Therefore, the outcome of conservative therapy for these patients is virtually unknown. The purpose of this study was to examine retrospectively the maternal and perinatal outcomes associated with the conservative management of 60 consecutive patients in whom severe preeclampsia occurred during the midtrimester (18 to 27 weeks' gestation).

Material and methods

From August 1, 1977, to July 31, 1984, 60 patients in whom severe preeclampsia occurred during the midtrimester (18 to 27 weeks' gestation) were delivered at the E. H. Crump Women's Hospital and Perinatal Center, Memphis, TN. Severe preeclampsia was defined as reported previously from this institution.[1] Thirty-four patients were first managed by local physicians and then referred to the Perinatal Center. The other patients were encountered and managed at the Perinatal Center. All patients had a live fetus at the time of admission to a hospital. Conservative management was attempted in each to prolong pregnancy until fetal lung maturity was achieved or until onset of either maternal or fetal complications (fetal death or fetal distress) occurred.

Initial management at local hospitals included bed

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rest, oral phenobarbital, methyldopa, hydralazine, and/or diuretics. Magnesium sulfate was used either intramuscularly or intravenously for about 24 hours in 20 patients. Those patients who had a favorable response to the initial therapy were continued on conservative treatment with the use of antihypertensive medications and phenobarbital. Patients were referred to the Perinatal Center whenever there was significant deterioration in either the maternal or fetal condition. Patients managed at the Perinatal Center were first treated with intravenous magnesium sulfate and hydralazine for 24 to 72 hours, and those who had a favorable response to the initial therapy were continued on conservative management. Oral methyldopa, with or without hydralazine, was administered to maintain diastolic blood pressure between 90 and 100 mm Hg. If diastolic blood pressure increased to above 110 mm Hg despite adequate oral antihypertensive medications, a continuous intravenous infusion of hydralazine was reinstituted.

All patients had laboratory evaluations as reported previously.[1] The combination of hemolysis, elevated liver enzymes, and low platelet count was defined as the "HELLP syndrome," as described by Weinstein.[4] Renal evaluation included serial measurement of creatinine clearance and 24-hour excretion of protein. Most patients had serial determinations of each of these tests. In addition, several women had measurements of catecholamines and metanephrine in 24-hour specimens of urine to rule out pheochromocytoma. Other patients had determinations of fluorescent antinuclear antibodies and lupus erythematosus cells to rule out systemic lupus erythematosus.

Management of patients first encountered at the Perinatal Center included intensive antepartum fetal surveillance by means of ultrasonography, antepartum fetal heart rate testing, and assessments of fetal pulmonary maturity. Serial ultrasonography was performed to monitor fetal growth. Starting as early as 27 weeks' gestation, serial (twice per week) nonstress testing and/or contraction stress testing were performed on all patients. In addition, when clinically indicated, a sample of amniotic fluid was obtained for determination of the lecithin/sphingomyelin (L/S) ratio and shake test to assess fetal pulmonary maturity. Intravenous magnesium sulfate (4 to 6 gm loading dose, followed by 1 to 3 gm/hr), with or without intravenous hydralazine, was used to stabilize the patients for a minimum of 4 hours before delivery. All patients with fetal death (n = 31) were delivered vaginally, with prostaglandin E_2 vaginal suppositories used to induce labor.

Clinical data on the infants included gestational age, birth weight, Apgar scores, and neonatal complications, as described previously.[1] An infant was considered to be small for gestational age if the birth weight was below the tenth percentile of the Lubchenco curve.[14] All newborn infants were followed until discharge from the intensive care nursery. For comparative purposes, a matched group of 29 premature infants who were delivered during the years 1978 through 1984, served as a control group for neonatal complications. These neonates were selected on the basis of gestational age, and month of birth during the study period. All neonates were delivered after premature labor and/or premature rupture of membranes. Mothers of the control neonates did not have any medical complications and were normotensive throughout pregnancy and labor; none had proteinuria. No patient received antihypertensive or tocolytic agents. The mothers were also matched for race and parity.

Results were analyzed by Student's *t* test to compare means of normally distributed data, χ^2 test to compare frequencies, and Fisher's exact test when the expected number in one cell was less than five. Differences were considered to be significant for P value <0.05.

Results

During the 7-year study period, there were 732 patients with severe preeclampsia and 168 with eclampsia among 49,452 deliveries. Sixty-four of these patients had onset of severe preeclampsia during the midtrimester. Four of the 64 had immediate delivery (three patients presented with abruptio placentae and fetal death, whereas the fourth had disseminated intravascular coagulation with twin gestation at 26 weeks). Thirty-six patients of the 60 (60%) were nulliparous, and 24 were gravida 2 or more. Forty-five patients (75%) were black, and 15 were white. The mean age (± 1 SD) was 23.9 ± 4.8 years, but 34 patients (57%) were less than 25 years of age. Fifty-four patients (90%) had prenatal care, and six (10%) had no prenatal care. Thirty-three patients (55%) had previously had chronic hypertension and/or renal disease prior to the present pregnancy (one had diabetes and one had sickle cell disease). The past obstetric history of the 24 patients with prior pregnancies was very poor. Seventeen patients (70%) had severe preeclampsia, two had eclampsia, three had abruptio placentae, and six had previous stillbirths.

Maternal outcome. No maternal deaths occurred during conservative management of these patients, but maternal morbidity was frequent, and, occasionally, life-threatening. Abruptio placentae was the most frequent complication, with an incidence of 21.7%. Twelve patients (20%) had thrombocytopenia, five patients (8.3%) had disseminated intravascular coagulation, and 10 patients (16.7%) had the HELLP syndrome during conservative management. Most of the hematologic abnormalities were associated with abruptio placentae

Table I. Pregnancy outcome

	Mean ± 1 SD	*Range*
Gestational age at admission (wk)	24.8 ± 1.9	18-27
Pregnancy prolongation (days)	11.4 ± 7.8	3-40
Gestational age at delivery (wk)	26.5 ± 1.9	20-30
Birth weight (gm)	671 ± 182	300-1250
Placental weight (gm)	186 ± 80	80-460

Table II. Fetal-neonatal weights (n = 60)

Category	*No.*	*%*
<500 gm	11	18
500-750 gm	28	47
751-1,000 gm	19	32
>1,000 gm	2	3
<25th percentile	58	97
<10th percentile	39	65

and fetal death. Ten patients (16.7%) developed convulsions, and three patients (5%) had acute renal failure and acute renal tubular necrosis. None of them required hemodialysis, and all three had normal renal function at the time of discharge from the hospital. Two patients with hypertensive encephalopathy developed the symptoms post partum, and both required infusions of nitroprusside to control hypertension. Neurological evaluation, including computerized axial tomography scans, was normal. Both patients were discharged without residual neurological deficit. Intracerebral hemorrhage occurred in one patient who was found to have a ruptured aneurysm of the right internal artery bifurcation. The aneurysm was surgically clipped, and the patient did not have any residual neurological deficit on follow-up. One maternal transfer patient was found to have a ruptured subcapsular hematoma of the liver 4 days after conservative management for severe preeclampsia at 23½ weeks' gestation. The hematoma was surgically evacuated after the patient was delivered of a stillborn infant. Her postoperative course was complicated by pulmonary edema and acute renal tubular necrosis. Recovery was spontaneous and she was discharged without any renal or hepatic deficits 17 days after admission.

Pregnancy outcome. Data on the weeks of gestation at the time of the patient's admission, the number of days pregnancy was prolonged, gestational age at delivery, and mean fetal and placental weights are summarized in Table I. Three patients (5%) had onset of severe preeclampsia at less than 20 weeks' gestation. Twenty-eight patients (47%) had onset between 21 and 25 weeks' gestation, and the other 29 patients (48%) had onset beyond 25 weeks' gestation. The 60 pregnancies resulted in 31 stillbirths and 21 neonatal deaths, for a perinatal mortality of 87%. When severe preeclampsia developed at 25 weeks or before, 23 of 31 pregnancies (74%) ended in fetal death, whereas the incidence of fetal death was 28% (eight of 29) when severe preeclampsia developed beyond 25 weeks' gestation ($p < 0.05$). Twenty-seven of the 31 stillbirths occurred prior to the start of antepartum fetal heart rate testing (prior to 27 weeks' gestation). Three of the 4 other patients with pregnancies that ended in fetal death had a reactive nonstress test 2 to 3 days prior to fetal death, and the fourth patient had a fetal death on the same day that she was scheduled to have the test. Two of these four stillbirths were associated with abruptio placentae.

The occurrence of fetal death with or without maternal complications was the most frequent indication for termination of conservative management. Antepartum fetal death was the indication for delivery in 31 patients (51%). Eight of the 31 pregnancies that ended in fetal death were associated with abruptio placentae, six with the HELLP syndrome, four with eclampsia, three with disseminated intravascular coagulation, and one with ruptured subcapsular hematoma of the liver. Thirteen of the 29 patients whose pregnancies resulted in live births were delivered because of antepartum fetal distress (nonreactive nonstress test plus positive contraction stress test, severe oligohydramnios). Twelve of the 13 infants in this group died within the neonatal period. Maternal complications were the indication for delivery in 13 patients (six had convulsions, three had abruptio placentae, two had disseminated intravascular coagulation, one had acute renal failure, and one had a ruptured cerebral aneurysm). The presence of mature lecithin/sphingomyelin ratio on amniocentesis was the indication for delivery in the other three patients.

Twenty-six (90%) of 29 patients with a live fetus at the time of delivery underwent cesarean section because of fetal distress, malpresentation, or uninducible cervix. Two patients had vaginal delivery subsequent to oxytocin induction in spite of fetal distress during labor (estimated fetal weight less than 600 gm). The other patient had a spontaneous vaginal delivery after spontaneous onset of labor. Twenty-eight of the live-born infants (97%) had an Apgar score of 4 or less at 1 minute; 26 infants (90%) had an Apgar score of 6 or less at 5 minutes. Table II summarizes the fetal-neonatal weights at the time of delivery. The clinical characteristics and neonatal outcome of study infants as compared with those of the control infants are summarized in Tables III and IV. Only two of the 60 infants (3%) had a birth weight above the twenty-fifth percentile, and 39 (65%) had a birth weight below the tenth percentile. Most of the small–for–gestational age infants (35 of 39) had symmetric fetal growth retardation (weight, length and head circumference well below tenth percentile). There was a significant difference in mean birth weight and frequency of small–for–gestational age infants between the study and control groups. The study group had lower birth weights and a higher incidence of small–for–gestational age infants. In addition, there was a significant difference between the two groups in regard to the frequency of cesarean section delivery and the level of Apgar scores at both 1 and 5 minutes (Table III). Neonatal complications were frequent in both study and control infants. There was a tendency for a higher incidence of respiratory distress syndrome in the study patients, but this difference was not statistically significant. However, there was a significant difference between the two groups in regard to neonatal mortality, which was much higher in the preeclamptic infants (72%).

Table III. Clinical characteristics of the infants

Characteristic	*Study* (*n* = 29)	*Control* (*n* = 29)
Gestational age (wk)	27.7 ± 1.0	27.7 ± 1.0
Birth weight (gm)*	719 ± 168	890 ± 164
Small for gestational age†	18/29	7/29
Cesarean section delivery†	26/29	6/29
Apgar score		
1 min ≤ 4†	28/29	19/29
5 min ≤ 6†	26/29	19/26

$*p < 0.05$.
$†p < 0.005$.

Table IV. Neonatal complications

Complication	*Study* (*n* = 29)	*Control* (*n* = 29)
Respiratory distress syndrome	11/29	6/29
Respiratory insufficiency prem.*	9/29	18/29
Pulmonary hemorrhage	10/29	6/29
Intracerebral hemorrhage	21/29	19/29
Neonatal seizures	5/29	4/29
Renal failure	4/29	3/29
Neonatal deaths*	21/29	12/29

$*p < 0.02$. All others not statistically significant.

The eight surviving infants stayed in the neonatal intensive care unit an average of 75 ± 15 days (range, 60 to 109 days). Four of the eight infants had bronchopulmonary dysplasia, two infants had hydrocephalus secondary to intraventricular hemorrhage, and two infants required anticonvulsive therapy for neonatal seizures at the time of discharge from the neonatal intensive care unit. Five of the eight surviving newborn infants were followed up to 3 years after discharge. Four of the five had normal physical and neurological development by that time, whereas the other infant was mentally retarded, with marked developmental delay, hearing loss, and seizure disorder. This infant had a ventriculoperitoneal shunt for hydrocephaly, required multiple hospitalizations, and was below the fifth percentile for both weight and height. Two infants were followed up to 9 months of age subsequent to discharge. Both infants had normal neurological development, but both are still below the tenth percentile by weight, length, and head circumference. The other infant has just been discharged from the neonatal unit.

Comment

The clinical course of severe preeclampsia is usually characterized by progressive deterioration in both maternal and fetal status. The ultimate goals of therapy must always be the safety of the mother first and then consideration for optimum perinatal outcome. Since the only cure for severe preeclampsia is delivery, this desired goal frequently forces the obstetrician to effect delivery in spite of fetal immaturity. However, in some cases, delivery may be delayed long enough for fetal maturation to be effected without injury to the mother. The success of such therapy usually depends upon the state to which the disease has progressed at time of initiation of this therapy. The timing of delivery in women who develop severe preeclampsia during the second trimester is a very difficult decision for every obstetrician. Immediate delivery will result in extremely high neonatal mortality[1, 5] whereas an aggressive attempt to delay delivery may expose the mother to severe morbidity and even mortality.[4, 9, 10] The potential benefit of improved neonatal outcome from delaying delivery must be balanced against the risks to the fetus of a potentially hostile and even life-threatening intrauterine environment.[1, 8] The fetus is usually at increased risk for sudden intrauterine death, and the resulting neonates are severely growth retarded, with multiple neonatal complications. In addition, the long-term outcome for such neonates is still unknown.

Some perinatal centers[15-17] have recently reported remarkable neonatal survival statistics for infants born in the late second trimester. Neonatal survival approaches 50% beginning as early as 25 weeks' gestational age in some centers. It should be noted that the likelihood of occurrence of major, reversible and irreversible, neonatal morbidity decreased with advanced gestational age. The results achieved in these centers reflect a general improvement in neonatal outcome for all gestational ages. However, the neonatal survival rate at any particular gestational age is never quite so good as that for the next older age group, even for 1 week's difference. These facts permit the superficially attractive conclusion that equates prolongation of pregnancy with improved perinatal survival in the individual case. This hypothesis is true, however, only if fetal loss in utero is significantly less than the postulated gain in neonatal survival. In addition, this hypothesis also assumes that prolongation of pregnancy in a potentially hostile environment improves the neonatal outcome a priori. The postulated improvement in neonatal outcome with increased gestational age may not occur in such an individual pregnancy.[2, 3, 7, 8] Furthermore, any improvement that might occur in neonatal outcome must be balanced against the potentially serious maternal risks.

Martin and Tupper[6] reported on 55 patients with severe preeclampsia before 36 weeks' gestation who were treated conservatively with bed rest, phenobarbital, and, occasionally, antihypertensive medications. However, only nine pregnancies were between 24 and 30 weeks' gestation, and most were at 29 to 30 weeks' gestation. This therapy increased mean gestational length by 23 days. Two of the nine pregnancies resulted in stillbirths, and one ended in neonatal death. Overall, marked intrauterine growth retardation (<2.5th percentile) occurred in 56.6%, asphyxia neonatorum was observed in 17%, and cesarean section was performed in 27% for fetal distress. Goodlin[2] reported on 28 women with severe preeclampsia whose condition was misdiagnosed, so that treatment was delayed. Six of these patients had onset of symptoms during the midtrimester (24 to 27 weeks), and none of the six survived. In a subsequent report, Goodlin et al.[3] reported on 11 white women with severe preeclampsia who were treated conservatively with plasma volume expansion. Four patients had onset of symptoms during the midtrimester (24 to 27 weeks). These four pregnancies resulted in five neonates (one set of twins), two of whom were stillborn, and one died in the neonatal period. d'Apice et al.[12] described three patients who were treated with plasma exchange for severe preeclampsia that occurred during the midtrimester (16 to 24 weeks). These pregnancies resulted in two infants who survived and one neonatal death. Similar treatment was used by Bayliss et al.[13] for a patient with severe preeclampsia at 26 weeks' gestation who was delivered of a live infant who survived.

Weinstein[4] reported on 29 patients with severe preeclampsia and the HELLP syndrome. Four of their pregnancies resulted in the birth of infants with weights less than 800 gm (probably midtrimester). Two of the four infants were stillborn, one died in the neonatal period, and one developed severe respiratory distress syndrome and bronchopulmonary dysplasia, but survived. Moore and Redman[7] reported on 24 patients with severe preeclampsia before 34 weeks' gestation who were treated conservatively with bed rest and antihypertensive therapy. All but one of the births were below the twenty-fifth percentile by weight, and 20 (83%) were below the tenth percentile. Four patients had onset of symptoms during the midtrimester that resulted in two stillbirths and two neonatal deaths.

Benedetti et al.[5] reported pregnancy outcome in 90 patients with severe preeclampsia who were delivered between January, 1978, and August, 1980. The number of patients who developed the disease during the midtrimester was not stated; however, all six stillborn infants reported weighed less than 751 gm. In addition, 13 infants had birth weights between 600 and 1,000 gm, and seven of the 13 died in the neonatal period. Lin et al.[8] reported fetal outcome in 157 hypertensive pregnancies, in 95 of which the pathologic diagnosis of preeclampsia was established by renal biopsy. Delivery in 11 of the 95 preeclamptic pregnancies occurred at less than 30 weeks' gestation, with perinatal death resulting in all of them. Most of the perinatal deaths were related to "intrauterine asphyxia" and abruptio placentae. Pritchard et al.[11] reported on 83 patients with antepartum eclampsia, four instances of which developed during the midtrimester (birth weight 490 to 750 gm). Two of the four cases resulted in stillbirths, and the other two ended in neonatal death.

The findings in the present study are compatible with those of an increased incidence of intrauterine growth retardation, abruptio placentae, fetal asphyxia, and acidosis in severe preeclampsia that occurs in the midtrimester. The hostile and unfavorable intrauterine environment may be responsible for all the stillbirths and most of the neonatal deaths. Fifty-eight of the 60 infants (97%) were below the twenty-fifth percentile by weight, and 39 (65%) were small for gestational age. It is important to note that intrauterine growth retardation was symmetric (affecting weight, length, and head circumference) in most of these infants. Moreover, 28 of the 29 live-born infants (97%) had an Apgar score of ≤4 at 1 minute, and 21 of 23 infants (90%) had a cord pH of less than 7.20. These findings may be attributed to apparent severe chronic uteroplacental insufficiency during prolongation of pregnancy. In view of the severe intrauterine asphyxia observed in these pregnancies, it is difficult to prove any benefit from prolonging such gestations. These results confirm the findings reported in several other studies.[2-8]

Neonatal complications in the study infants were frequent (Table IV), but similar complications were also encountered in the control infants of similar gestational age. However, the study group had a higher incidence of SGA infants, higher frequency of low Apgar scores at 1 and 5 minutes, and higher incidence of neonatal deaths. This difference in neonatal survival rates between the study and control infants might be related to differences in the condition of the neonates at the time of delivery. This finding is in agreement with those of Yu et al.[17] for infants born at 24 to 26 weeks' gestation. Yu et al. found a significant difference in mean Apgar scores at 1 and 5 minutes, as well as in admission pH, between infants who survived and infants who died in the neonatal period (those who died had lower mean Apgar scores and lower admission pH). In fact, a neonatal survival rate of 28% (eight of 29) in the study infants is well below the expected survival rate (63% to 70%) in infants of similar gestational age reported by others.[15-17] The above-mentioned findings argue against any benefit to the neonate from prolongation of gestation in severely preeclamptic pregnancies. In addition, an overall perinatal survival rate of 13% is "poor at best" and does not indicate any benefit from prolonging gestation in such pregnancies.

Our findings indicate that conservative management in such pregnancies is associated with high maternal morbidity. Thirteen of the 60 patients (22%) had abruptio placentae, 10 patients (17%) developed convulsions, and a few patients developed life-threatening complications, such as hypertensive encephalopathy, intracerebral hemorrhage, and ruptured subcapsular hematoma of the liver. We attribute most of these maternal complications to delayed delivery in such pregnancies. Such maternal complications are not encountered so frequently in severely preeclamptic patients delivered immediately after maternal stabilization.

In consideration of the frequency of maternal and perinatal complications described above, conservative management can be justified in only a limited number of clinical situations. These cases should be selected primarily on the basis of the clinical estimation of the fetus' chances for extrauterine survival. Since neonatal survival rates are most closely related to gestational age and birth weight, these two factors must be carefully assessed prior to deciding on the plan for clinical management. Therefore, a thorough ultrasonographic examination with estimation of fetal weight is mandatory for all candidates for the conservative approach.

In summary, the results of this retrospective, case control study do not support the use of conservative management for pregnancies complicated by severe preeclampsia in the second trimester. For the 60 cases reviewed in this study, conservative management did not significantly improve perinatal outcome. In addition, the prolongation of these pregnancies was associated with a high rate of maternal morbidity. Thus, in the present series, the risks of morbidity for the mother seemed to outweigh the potential benefits of improved outcome for the infants. Because of the retrospective nature of this study, we cannot unequivocally conclude that conservative management is of no value. However, until the safety and efficacy of this approach are evaluated with additional prospective, controlled studies, it is advisable to avoid conservative management for these pregnancies.

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Urethral isolation of the genital mycoplasmas and *Chlamydia trachomatis* in women with chronic urologic complaints

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Eighty-six abacteriuric women with chronic urologic complaints were studied to determine the relationship of *Chlamydia trachomatis, Mycoplasma hominis,* and *Ureaplasma urealyticum* to their symptoms or diagnoses. All patients had urethral scrape specimens for isolation of the three organisms as well as a detailed urologic history and urodynamic evaluation. Thirty-three of 86 patients (38%) had positive urethral ureaplasma cultures; seven had concurrent *M. hominis* isolation. No patient had *M. hominis* as the only urethral isolate and none had a positive *C. trachomatis* culture. There were no significant differences in urologic symptoms or in urodynamic diagnoses between *Ureaplasma* culture-positive and culture-negative subjects. It was also found that colonization of the urethra with *Ureaplasma* decreased with increasing age and with hypoestrogenism. (AM J OBSTET GYNECOL 1985;152:38-41.)

Key words: Female urology, infection, urethra

Urethral syndrome is an imprecisely defined clinical entity of uncertain etiology that is usually a diagnosis of exclusion. The diagnosis traditionally has been entertained when symptoms suggesting a lower urinary tract infection (that is, frequency, urgency, or dysuria) are present in a woman who has no significant bacterial growth on urine culture.[1] If local bladder and urethral disease and detrusor instability are excluded the diagnosis has been considered firmly established.[2,3] The entity can be divided clinically into acute and chronic urethral syndrome. Women with acute urethral syndrome usually present within several days of the abrupt onset of symptoms, having been asymptomatic previously. In contrast, patients with chronic urethral syndrome typically have had symptoms for many months or years, some being unable to recall ever being asymptomatic.

Recently several large segments of the acute urethral syndrome population have been identified as having distinct, diagnosable infectious etiologies for their symptoms. The significance of low-growth (as low as 10^2 colony forming units per milliliter) coliform cultures in symptomatic women has been convincingly demonstrated by Stamm et al.[2] These same investigators have further identified *Chlamydia trachomatis,* the leading causative agent of nongonococcal urethritis in men, and *Staphylococcus saprophyticus* as probable causes of acute urethral syndrome.[2-4] The evidence linking the genital mycoplasmas, particularly *Ureaplasma urealyticum,* with nongonococcal, nonchlamydial urethritis in men has become more and more convincing.[5] Although the evidence is not so convincing, it has been suggested that *U. urealyticum* may also be responsible for some cases of acute urethral syndrome in women.[6]

Advances in explaining some portion of chronic urethral syndrome cases have also been reported. As simultaneous urethrocystometry has been more widely used in urodynamic evaluations, the syndrome of unstable urethral pressure has been recognized more frequently in women with chronic urethral syndrome.[7,8] The role played in chronic urethral syndrome by the microorganisms recently implicated as possible etiologic agents for acute urethral syndrome is undefined. The aim of this study was to define the role played by *C. trachomatis* and the genital mycoplasmas, *Mycoplasma hominis* and *U. urealyticum,* in a population of abacteriuric women with chronic urologic symptoms.

Methods

Study population and design. The study population consisted of 86 new referral patients with chronic lower urinary tract symptoms studied in the Gynecologic Urodynamic Testing Clinic during an 18-month period ending in September, 1983. The women ranged in age from 17 to 70 years and all had negative (no-growth) midstream clean-catch bacterial urine cultures prior to urodynamic evaluation. Urologic complaints were recorded by use of a standardized questionnaire with extensive interview supplementation by one or both of us. A complete genitourinary physical examination, including an appropriate evaluation for vulvovaginal infection, was performed prior to the urodynamic evaluation. Patients who had positive cultures for *M. hominis* or *U. urealyticum* were not treated with antibiotics.

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Table I. Culture results versus symptoms and diagnoses

	U. urealyticum–*negative* ($n = 53$)		U. urealyticum–*positive* ($n = 33$)		
	n	%	n	%	p
Symptom					
Dysuria	6	11	3	9	NS
Frequency	18	34	14	42	NS
Urgency	41	77	25	76	NS
Diagnosis					
Stress urinary incontinence	28	53	15	46	NS
Idiopathic detrusor instability	12	23	10	30	NS
Sensory urgency	21	40	10	30	NS
Unstable urethral pressure–vesicosphincter dyssynergia	8	15	8	24	NS

Urodynamic methods and diagnostic criteria. Cystometry was performed with retrograde filling via a transurethral catheter. For the first 4 months of the study period, carbon dioxide was the infusion agent with an infusion rate of 120 ml/min. Bladder pressures were measured on a single-channel carbon dioxide cystometer (Browne Corp., Carpinteria, California). For the remainder of the study, room-temperature saline solution was used as the infusion agent with infusion rates of 30 to 50 ml/min. From the fifth through the fifteenth month of the study, simultaneous rectal, bladder, and subtracted detrusor pressures were recorded by means of water transducers and a multiple-channel uro dynamic recorder (Life-Tech Instruments, Houston, Texas). During the final 3 months of the study, simultaneous rectal, bladder, and maximum urethral pres sures were recorded by means of Fr 8 dual-channel mi crotip transducer catheters (Millar Instruments, Hous ton, Texas). Cystometry was performed with the patient sitting and standing; urethrocystometry was performed with the patient in a modified lithotomy position with 45 degrees of reverse Trendelenburg. All cystometric evaluations included provocative maneuvers (coughing or heel bouncing).

Simple fluid-weight uroflowmetry was performed prior to any instrumentation, by use of a commode chair and load-cell flow transducer (Life-Tech Instruments). Complex uroflowmetry was performed after cystometry, with rectal pressures recorded via a balloon-tipped catheter connected to a water pressure transducer and bladder pressures measured by either an Fr 3 water catheter connected to a water pressure transducer or by an Fr 3 microtip pressure transducer catheter (Millar Instruments). Urethral sphincter skeletal muscle electromyography was added to urethrocystometry and complex uroflowmetry studies in selected patients. Direct electromyography was performed by Teflon-coated unipolar needle electrodes inserted submucosally in the periurethral area, recorded on urodynamic recorder chart paper, and monitored with an audio monitor (Life-Tech Instruments). Urethral pressure profilometry was performed with either carbon dioxide pressure transducers or microtip transducer catheters. Direct-view carbon dioxide urethroscopy was performed with an Fr. 24 Robertson endoscope (Browne Corp.) after all other urodynamic studies were completed. The urethroscope was introduced and advanced atraumatically under direct vision with the flow of carbon dioxide used to open the urethra ahead of the advancing endoscope. All urodynamic evaluations were performed by one or both of us. All urethral manipulations were performed with a sterile technique following antiseptic preparation of the periurethral vestibule.

Stress urinary incontinence, bladder instability (idiopathic detrusor instability), and sensory urgency were defined according to the recommendations of the International Continence Society Committee for Standardization of Terminology[9] and were diagnosed with cystometry. Vesicosphincter dyssynergia was defined according to the recommendations of the same committee and was diagnosed with simultaneous urethrocystometry and sphincter electromyography[10] and/or complex uroflowmetry. Unstable urethral pressure was defined as variations in the urethral pressure >15 cm of water not associated with an increase in intra-abdominal pressure or with vascular pulsations[7] and was diagnosed with simultaneous urethrocystometry.

Microbiologic methods. At the conclusion of the urodynamic evaluation, a sterile cotton swab was inserted into the urethra to the urethrovesical junction, rotated to gently abrade the mucosa, removed, and extracted immediately into 0.2 mol/L of sucrose–phosphate buffer transport medium. The inoculated medium was transported on ice to the Clinical Microbiology Laboratory and stored at −80° C until cultured. All specimens were cultured within 4 days. The presence of *C. trachomatis* was determined by examination of cycloheximide-treated McCoy cell tissue cultures that had been inoculated with 0.1 ml of the extracted specimen and subjected to either iodine staining (first 9 months of the study) or direct monoclonal immunofluorescence staining (last half of the study).[11] A7 agar plates and U9B broth were inoculated with 0.2 ml of the extracted specimen. *U. urealyticum* and *M. hominis* were detected by evaluating both pH indicator changes in U9B broth and the morphologic features of colonies on A7 agar plates.[12, 13]

Analysis of data. Data were analyzed for significance with the χ^2 test with the Yates correction or a two tailed *t* test.

Results

Sixty-nine (80%) of the 86 patients complained of one or more of the classical triad of symptoms associated with urethral syndrome. Sixty-six (77%) reported urgency, 32 (37%) frequency, and nine (10%) dysuria. Eight (9%) reported all three symptoms, 23 (27%) two symptoms, 38 (44%) a single symptom, and 17 (20%) none of the three symptoms. The majority of referred patients, 58 of 86 (67%), also complained of the symptom of stress urinary incontinence.

The urodynamic diagnoses in the 86 patients were as follows: stress urinary incontinence, 50% (43); sensory urgency, 36% (31); idiopathic detrusor instability, 265 (22); and unstable urethral pressure/vesicosphincter dyssynergia, 19% (16). Twenty-seven subjects had more than one abnormal urodynamic diagnosis, with 25 having two and two having three abnormal diagnoses. Four subjects had completely normal urodynamic evaluations.

Cultures of 53 (62%) of the subjects grew none of the three organisms and 33 (38%) grew *U. urealyticum.* Cultures of seven subjects (8%) had *M. hominis* isolated concurrently with *U. urealyticum.* None of the cultures grew *M. hominis* alone and none of the subjects had a positive *C. trachomatis* culture.

There was no significant difference in the incidence of any of the three urethral syndrome symptoms or of the four urodynamic diagnoses between the *U. urealyticum* culture-positive and the culture-negative patients (Table I). Likewise the incidence of urethroscopic evidence of chronic urethral or trigonal inflammation (inflammatory polyps, exudate, epithelial shagginess) in culture-positive subjects (six of 23, 26.1%) was not significantly different than that in culture-negative subjects (10 of 41, 24.4%).

The mean age of culture-negative patients (44.9 years, SD = 9.6) was significantly higher than the mean age of culture-positive patients (36.2 years, SD = 13.4; $p < 0.01$). Culture-negative patients were significantly more likely to be hypoestrogenic (postmenopausal or castrate and receiving no exogenous estrogen) than culture-positive patients, 34% (18 of 53) versus 3% (one of 33), respectively ($p < 0.005$).

Comment

The role of *C. trachomatis* in the genesis of acute urethral syndrome is well established. Between 25% and 50% of acute urethral syndrome in women with negative bacterial urine cultures can be attributed to chlamydia.[3] Therapy with doxycycline has been shown significantly more effective than placebo in eradicating the organism as well as symptoms and pyuria in women with acute urethral syndrome.[4] This well-established association and the knowledge that chlamydia displays a substantial degree of latent or inapparent infections in all natural hosts at many different anatomic sites makes infection with the organism a reasonable consideration in women with more chronic or indolent urinary symptoms. The finding that none of 86 abacteriuric women in this study had chlamydia isolated from the urethra suggests that *C. trachomatis* is not a common cause of chronic lower urinary tract complaints or dysfunction.

The evidence linking the genital mycoplasmas with nongonococcal nonchlamydial urethritis in men has been exhaustively reviewed by Taylor-Robinson et al.[5, 6] It can be concluded that *U. urealyticum* but not *M. hominis* causes a portion of nongonococcal urethritis, although a variety of reasonable explanations must be evoked to explain the ubiquity of ureaplasma compared to the relative infrequency of urethritis. Although a relationship has been suggested between ureaplasma and acute urethral syndrome in women,[6] some reports have shown no relationship qualitatively[3, 14] or quantitatively[3] between the organism and lower urinary tract symptoms. The current series demonstrates no significant difference in the incidence of any chronic urologic symptom or urodynamic diagnosis between patients with positive urethral ureaplasma cultures and those with negative cultures.

The incidence of urethral *U. urealyticum* isolation in this report (38%) is slightly lower than that of two other published series (48% to 58%).[3, 14] However, our premenopausal prevalence of ureaplasma (48%) is in agreement. The mean age of patients was reported in only one of the previous series[3] and was significantly lower (25 years, range 18 to 39) than in our series (41.5 years, range 17 to 70). The significantly lower incidence of ureaplasma isolation from hypoestrogenic subjects in our study is supported by the decreased incidence of isolation after menopause in two other series.[15, 16] It has also been noted that neonatal colonization with ureaplasma tends not to persist,[5] further suggesting an association between estrogen status and ureaplasma isolation. The significantly lower mean age of subjects with positive ureaplasma cultures in this series may simply be another reflection of hormonal status or may reflect age-related differences in sexual activity. It is well accepted that ureaplasma colonization is virtually limited to sexually active individuals and that the incidence of colonization increases with increasing numbers of sexual partners.[5] The current study did not determine the interrelationship between age, sexual activity, and estrogen status so that the relative contribution of any one of these parameters to urethral ureaplasma colonization rates cannot be assessed.

In conclusion, there were no significant differences in urologic symptoms or in urodynamic diagnoses between *U. urealyticum* urethral culture-positive and culture-negative patients in a group of 86 subjects with chronic urologic complaints and negative bacterial urine cultures. Further no subject had *C. trachomatis* isolated from the urethra. Finally, colonization of the urethra with ureaplasma decreases with increasing age and with hypoestrogenism.

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Genital tuberculosis in an elderly woman with the primary symptoms of pelvic prolapse: Case report

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A case of symptomatic pelvic relaxation resulting from complications secondary to genital tuberculosis is presented. (AM J OBSTET GYNECOL 1985;152:42-3.)

Key words: Tuberculosis, genital prolapse

It is well known that female genital tuberculosis is one of the secondary manifestations of pulmonary tuberculosis, which frequently is first evidenced as infertility, pelvic pain, and menstrual irregularities.

We report here the case of a patient with genital tuberculosis whose primary complaints were those of pelvic relaxation.

Case report

M. P., a 66-year-old Mexican woman, para 10, gravida 10, entered the gynecology clinics of Los Angeles County–University of Southern California Medical Center, complaining of a 10-year progressive history of vaginal fullness and uterine descensus. She complained of chronic constipation, requiring splinting for defecation. She denied having postmenopausal bleeding or stress urinary incontinence and was not sexually active. She had no nocturnal diaphoresis, weight loss, or other genitourinary or gastrointestinal symptoms. Her last menstrual period was about 20 years prior to examination.

Her past medical history revealed no menstrual irregularities. Her deliveries occurred at home, with the largest infant weighing 4500 gm. The patient had a negative skin test for tuberculosis 8 years prior to examination. This was her first pelvic examination by a physician.

On physical examination she was found to be a normal tensive, afebrile elderly woman in good health. Weight was 143 pounds, chest was clear to auscultation and percussion, and abdomen was nondistended and nontender. Pelvic examination revealed a moderate cystocele and severe rectocele with perineal breakdown. Uterine descensus to within 2 cm of the introitus was noted when the patient performed the Valsalva maneuver in the supine position. However, no enterocele was discernible. The uterus was normal in shape, size, and consistency and was freely mobile. Adnexa were normally tender without palpable masses. The diagnosis of symptomatic pelvic prolapse was made, and a preoperative workup was begun. The patient's chest x-ray findings were within normal limits without scarring or were consistent with granulomatous disease. Hematocrit value was 39%; white blood cell count was 10,000/ml with a normal differential and no eosinophils present. SMA 12 panel and prothrombin panel evaluations were within normal limits.

The patient was taken to the operating theater for a vaginal hysterectomy and anterior and posterior colporrhaphy. Examination under anesthesia confirmed the preoperative findings of pelvic prolapse. Upon entry into the posterior cul-de-sac 175 ml of milky serous fluid extruded from the defect and was sent for cytologic evaluation. Digital examination of the cul-de-sac showed multiple, raised, 0.5 by 0.5 cm peritoneal implants that covered the adhesion-free right adnexa. The left adnexa was similarly covered as well as markedly adherent to the lateral pelvic side wall and was covered with thick adhesions. No masses were noted.

A frozen-section biopsy of a 3 by 2 cm strip of cul-de-sac peritoneum showed granulomatous disease, consistent with tuberculosis. The colpotomy defect was closed with a single layer of No. 0 chromic suture and the procedure terminated.

A postoperative purified protein derivative skin test was positive (5 by 3 cm at 24 hours). Peritoneal fluid was negative for acid-fast bacilli, and the final section of the pathology specimen confirmed the presence of casseous granulomatous disease, consistent with the diagnosis of tuberculosis. Postoperatively the patient stated that her symptoms of vaginal fullness had significantly decreased, but she continued to complain of constipation requiring splinting for successful defecation. Cultures of the granulomata were positive for *Mycobacterium tuberculosis,* which is sensitive to isoniazid and rifampicin. After the patient completes her 6-month preoperative treatment with these drugs, she will undergo total vaginal hysterectomy and anterior-posterior colporrhaphy with layered perineal repair.

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Comment

Nichols and Randall[1] state that genital prolapse may result when normal pelvic supports are subjected to chronic increases in intra-abdominal pressure or when defective genital support (either congenital or acquired) is subjected to even normal intra-abdominal pressure. In this patient the prolapse was of combined origin, with both a structural abnormality (probably secondary to birth trauma) and an increased intra-abdominal pressure (related to her ascites secondary to peritoneal inflammation).

Since this patient lacked the classic symptoms of genital tuberculosis, the disease was an unexpected finding. Yet it is important to note that a negative x-ray finding cannot rule out the possibility of genital tuberculosis. The majority of the pulmonary lesions are arrested and not evident on x-ray film. Indeed, the most common radiographic abnormalities in patients with genital tuberculosis are found on hysterosalpingography.[2]

This case illustrates that any process that increases intra-abdominal pressure (i.e., intra-abdominal masses, chronic cough, ascites, which may be malignant, infectious, or secondary to hepatic disease) may worsen the symptoms accompanying genital prolapse. The symptoms of genital prolapse may be relieved if damage to the supporting ligaments and pelvic diaphragm has not become irreversible.

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Use of ultrasound in antenatal diagnosis of large–for–gestational age infants in diabetic gravid patients

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Near-term ultrasonograms of 44 diabetic gravid patients and 47 nondiabetic gravid patients were retrospectively analyzed. The mean values of abdominal diameter to femur length ratios and abdominal diameter to biparietal diameter ratios in diabetic gravid patients with large–for–gestational age fetuses were significantly different from those values in diabetic patients with appropriate–for–gestational age fetuses and in nondiabetic patients. Glycosylated hemoglobin values were above 7.4% (mean ± 2 SD) in 79% of diabetic patients with large–for–gestational age infants and abdominal diameter to femur length ratio exceeding 1.385. Glycosylated hemoglobin values were ≤7.4% in 69% of diabetic gravid patients with appropriate–for–gestational age fetuses and abdominal diameter to femur length ratio less than 1.385. These findings suggest that large–for–gestational age infants have a different growth characteristic with a disproportionate enlargement of the abdomen. This possibly results from a long period of elevated levels of maternal plasma glucose (as shown by elevated values of glycosylated hemoglobin). (AM J OBSTET GYNECOL 1985;152:43-7.)

Key words: Diabetes, pregnancy, fetal growth, ultrasonogram

The diagnosis of a large–for–gestational age (LGA) fetus is an important and at times a difficult clinical task. Numerous investigators[1-3] have attempted with varying success to correlate intrauterine fetal measurements and birth weights. Exposure to elevated maternal levels of blood glucose and, subsequently, fetal levels of insulin is known to result in accelerated fetal growth in diabetic gravid patients.[4-6] In a series by O'Shaughnessy et al.,[7] approximately 50% of the diabetic pregnancies resulted in LGA infants. These infants have a higher neonatal morbidity and mortality rate than that of appropriate–for–gestational age (AGA) infants, as a result of stress and trauma incurred during parturition.

High values of glycosylated hemoglobin (HbA_1) have been associated with poor control of levels of blood

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Table IA. Demographic characteristics of patients

	Patients with LGA fetuses			*Patients with AGA fetuses*		
	Diabetic (n = 24)	*Nondiabetic (n = 26)*	*p*	*Diabetic (n = 20)*	*Nondiabetic (n = 21)*	*p*
Parity	1.58 ± 1.14	1.19 ± 1.3	NS	1.05 ± 0.76	1.67 ± 1.2	<0.05
Age (yr)	31.92 ± 5.87	26.4 ± 5.25	<0.001	26.25 ± 4.72	27.81 ± 5.72	NS
Birth weight (gm)	4171.3 ± 446	4165.8 ± 254	NS	3282.3 ± 392	3232.4 ± 257	NS
Gestational age (wk)	35.3 ± 2.55	36.2 ± 3.04	NS	36.2 ± 3.15	36.1 ± 2.02	NS

Table IB. Distribution of diabetic patients according to White's classification

Classification	*Patients with LGA fetuses*	*Patients with AGA fetuses*
A	12	12
B	8	4
C	2	3
D and R	2	1
Total	24	20

glucose.[8] Determination of glycosylated hemoglobin has been proposed as a test for detecting pregnant diabetic patients who are at risk of delivering large infants.[9, 10] Measurements of femur length, which has been used as an alternative parameter for assessing fetal growth, appears to be equally as reliable as, or perhaps more reliable than, biparietal diameter in the assessment of gestational age in the third trimester.[11] In the present study, we attempted to differentiate the growth characteristics of LGA fetuses of diabetic gravid patients from those of nondiabetic gravid patients.

Material and methods

A retrospective analysis was made of the ultrasonograms of 47 diabetic gravid patients who delivered over a period of 2 years (July, 1980, to June, 1982). Availability of HbA_1 values in the third trimester and confirmed gestational age were considered to be prerequisites for selection of these patients. Suspected macrosomia and confirmation of gestational age or suspected abnormal presentation were the indications for obtaining these ultrasonograms.

The criteria of Brenner et al.[12] were used to assign the growth percentiles of these infants. Infants who weighed between the tenth and ninetieth percentiles were considered to be AGA, and those with body weights above the ninetieth percentile were considered to be LGA.

Control patients were selected from labor room records and ultrasonogram files. These patients had undergone ultrasonographic evaluation for a variety of indications, such as suspected macrosomia, confirmation of gestational age prior to elective cesarean section, suspected malpresentation, and placental localization. The selection criteria included confirmed gestational age by history, early examination, and neonatal examination in some, and normal carbohydrate tolerance. Only the patients who nearly matched the diabetic group according to age, parity, and gestational age in AGA and LGA groups were finally selected as a control group for analysis. The demographic characteristics of these patients are presented in Tables IA and IB.

A real-time linear array scanner with a 3.5 MHz frequency transducer and a velocity set at 1,540 m/sec was used to measure the biparietal diameter, abdominal diameter, and femur length. The biparietal diameter was measured at the level of the thalamus, and the abdominal diameter at the level of the umbilical vein, perpendicular to the fetal spine. The biparietal diameter and abdominal diameter measurements were made from the outer to the inner edges. The femur length consisted of the largest measurement along the bone shaft. The ratio of abdominal diameter to femur length and that of abdominal diameter to biparietal diameter were calculated in all fetuses. The sonograms were obtained up to 8 weeks prior to delivery, and the mean sonogram-to-delivery interval was 20 days. In 75% of diabetic gravid patients and 68% of nondiabetic gravid patients, sonograms were obtained within 4 weeks of delivery. For the purpose of analysis, the patients were divided into four groups: LGA diabetic (group 1), AGA diabetic (group 2), LGA nondiabetic (group 3), and AGA nondiabetic (group 4).

The results were analyzed by two-tailed *t* tests, and χ^2 calculations. The determinations of optimum cutoff points for abdominal diameter/femur length and abdominal diameter/biparietal diameter values which provided the best composite with reference to sensitivity and specificity were accomplished with the use of receiver operating characteristic curves. Values tested were from 1.35 to 1.45 for abdominal diameter/femur length and 1.0 to 1.1 for abdominal diameter/biparietal diameter ratios. HbA_1 was measured by cation-exchange column chromatography (Isolab, Akron, Ohio).

Results

The mean values of abdominal diameter/femur length and abdominal diameter/biparietal diameter ra-

Table II. Comparison of abdominal diameter/femur length ratios (mean ± SD) in diabetic and nondiabetic fetuses

Group 1 LGA diabetic (1.44 ± 0.09) (n = 24)	*Group 2* AGA diabetic (1.35 ± 0.06)	(n = 20)	$p < 0.001$
	Group 3 LGA nondiabetic (1.37 ± 0.09)	(n = 26)	$p < 0.01$
	Group 4 AGA nondiabetic (1.31 ± 0.07)	(n = 21)	$p < 0.001$

Statistical test: Two-tailed *t* test.

Table III. Comparison of abdominal diameter/biparietal diameter ratios (mean ± SD) in diabetic and nondiabetic fetuses

Group 1 LGA diabetic (1.12 ± 0.08) (n = 24)	*Group 2* AGA diabetic (1.05 ± 0.06)	n = 20	$p < 0.01$
	Group 3 LGA nondiabetic (1.07 ± 0.07)	n = 26	$p < 0.01$
	Group 4 AGA nondiabetic (1.02 ± 0.06)	n = 21	$p < 0.001$

Statistical test: Two-tailed *t* test.

Table IV. Abdominal diameter/femur length ratios in AGA and LGA fetuses of diabetic gravid patients

Abdominal diameter/femur length ratio	*Group 1 AGA fetus*	*Group 2 LGA fetus*
>1.385	4	19
≤1.385	16	5
Total	20	24

$\chi^2 = 15.31$, $p < 0.005$

Sensitivity for detection of LGA fetuses	79%
Specificity for detection of LGA fetuses	80%
Predictive value of an abnormal ratio	83%
Predictive value of a normal ratio	76%

Table V. Abdominal diameter/biparietal diameter ratios in AGA and LGA fetuses of diabetic gravid patients

Abdominal diameter/biparietal diameter ratio	*Group 1 AGA fetus*	*Group 2 LGA fetus*
>1.065	8	20
≤1.065	12	4
Total	20	24

$\chi^2 = 8.84$, $p < 0.005$

Sensitivity for detection of LGA fetuses	83%
Specificity for detection of LGA fetuses	60%
Predictive value of an abnormal ratio	71%
Predictive value of a normal ratio	75%

Table VI. Relationship of glycemic control (HbA$_1$) to abdominal diameter/femur length ratio in diabetic gravid patients with LGA and AGA fetuses

Abdominal diameter/femur length ratio	*Group 1 LGA fetuses*		*Group 2 AGA fetuses*		
	↑ *HbA$_1$**	*N HbA$_1$*	↑ *HbA$_1$**	*N HbA$_1$*	*Total*
>1.385	15	4	1	3	23
≤1.385	2	3	5	11	21

$\chi^2 = 17.27$, $p < 0.005$.
*Mean ± 2 SD = >7.4%.

tios in group 1 were significantly higher than those in groups 2, 3, and 4 (Tables II and III). There were no differences between the abdominal diameter/femur length or abdominal diameter/biparietal diameter ratio values in groups 2, 3, and 4.

In 19 of 24 fetuses in group 1 and in four of 20 fetuses in group 2, the abdominal diameter/femur length ratio was above 1.385 (Table IV). Furthermore, in only eight nondiabetic patients with LGA fetuses and in four nondiabetic gravid patients with AGA fetuses did the abdominal diameter/femur length ratio exceed 1.385. Also, 20 of 24 fetuses in group 1, as opposed to eight of 20 in group 2, 12 of 26 in group 3, and five of 21 in group 4, had an abdominal diameter/biparietal diameter ratio greater than 1.065 (Table V). By the use of abdominal diameter/femur length and abdominal diameter/biparietal diameter ratios together, the false negative rate was reduced to 8%.

The disproportionate enlargement of the abdomen in the fetuses of group 1 seems to have resulted from an elevated mean level of plasma glucose as depicted by elevated levels of HbA$_1$ (Table VI).

Comment

Several investigators have used ultrasound to evaluate fetal growth, but few have addressed the accuracy of sonographic prediction of fetal outcome in diabetic pregnancies. Elliot et al.[13] performed a retrospective analysis of diabetic gravid patients who underwent ultrasound assessment within 3 weeks of delivery. Those authors, in an effort to predict fetal macrosomia, developed a macrosomic index by subtracting the biparietal diameter from the chest diameter. Eighty-seven percent of the infants who weighed more than 4,000 gm had a macrosomic index of 1.4 cm or greater. However, only 61% of the fetuses screened as positive by a macrosomic index of 1.4 cm or more were truly macrosomic, thus giving the index a low predictive value. Ogatta et al.[14] demonstrated that all diabetic gravid patients with fetal abdominal circumference growth greater than 2 SD delivered infants larger than those with normal abdominal circumference growth. The present study suggests that the LGA fetuses of diabetic gravid patients seem to have disproportionate accelerated abdominal growth when compared to LGA and AGA fetuses of nondiabetic gravid patients and AGA fetuses of diabetic gravid patients, as demonstrated by higher mean ultrasonic abdominal diameter/femur length and abdominal diameter/biparietal diameter ratio indices in the third trimester. Furthermore, an abdominal diameter/femur length ratio greater than 1.385 and an abdominal diameter/biparietal diameter ratio greater than 1.065 have high predictive value for detecting fetuses of diabetic gravid patients destined to develop macrosomia. On the other hand, these ratios cannot differentiate genetically predisposed LGA fetuses from AGA fetuses.

Five LGA fetuses of diabetic mothers in the present study had abdominal diameter/femur length ratios of less than 1.385. In three of these five fetuses, the sonogram-to-delivery intervals exceeded 4 weeks, and the maternal HbA_1 values were less than 7.4% at the time of sonography. The long sonogram-to-delivery interval in the presence of normal HbA_1 values could explain that, at the time of scanning, these fetuses had not been exposed long enough to a hyperglycemic state to cause disproportionate overgrowth. However, subsequent to these ultrasonograms, two of the three patients had elevated levels of HbA_1. Of the other two patients with short sonogram-to-delivery intervals, one had normal HbA_1 values throughout pregnancy. This could possibly indicate a genetic component rather than an abnormal carbohydrate metabolism leading to excessive fetal growth. Only one patient had an abdominal diameter/femur length ratio less than 1.385 despite an elevated HbA_1 value (9.6%) and short sonogram-to-delivery interval. In four AGA fetuses of diabetic mothers, the abdominal diameter/femur length ratio was equal to or greater than 1.385. The sonogram-to-delivery interval was less than 4 weeks in all these patients; and the HbA_1 values were also normal in three of them. These false positive results could be either biologic deviations or technical errors. Four LGA fetuses of diabetic mothers had an abdominal diameter/biparietal diameter ratio equal to or less than 1.065. Three of the four also had false negative abdominal diameter/femur length ratios. Eight AGA fetuses of diabetic mothers had abdominal diameter/biparietal diameter ratios greater than 1.065. All patients had short sonogram-to-delivery intervals, and four had false positive abdominal diameter/femur length ratios. Maternal HbA_1 values were elevated in two cases. The higher number of false positive abdominal diameter/biparietal diameter ratios than abdominal diameter/femur length ratios could have been due to compression of the fetal head in deeply engaged vertex or breech presentations. The abdominal diameter/femur length ratio of 1.385 appears to have a better discriminating value than the abdominal diameter/biparietal diameter ratio of 1.065 for selecting LGA fetuses of diabetic gravid patients. Both ratios have similar sensitivities, but the abdominal diameter/femur length ratio has a higher specificity and predictive value.

Since the salient feature in LGA fetuses of diabetic gravid patients is accelerated abdominal growth, serial measurements of the fetal abdomen should predict LGA infants, as proposed by Ogatta et al.[14] Reliance on serial abdominal measurements alone requires exact knowledge of gestational age, and a large proportion of our patient population has uncertain dates. Usage of ratios thus could enable detection of accelerated abdominal growth in patients with uncertain dates. Hadlock et al.[15] have shown that a ratio of femur length and abdominal circumference is independent of gestational age and have recommended it for fetal assessment in patients with uncertain dates who are at risk for intrauterine growth retardation. In the present study, we used the single measurement of abdominal diameter instead of using abdominal circumference measured by planimetry or formula with the use of two diameters

$$(d_1 + d_2) \times 1.57.^{16}$$

This was carried out because the single measurement of abdominal diameter was included in most standard sonographic evaluations. Ultrasonic measurement of abdominal diameter/femur length and abdominal diameter/biparietal diameter ratios seems to be a valuable adjunct in the prediction of LGA infants in diabetic gravid patients. Furthermore, with the use of these ratios it was possible to differentiate the growth characteristics of LGA infants of diabetic mothers from those of LGA infants of nondiabetic mothers.

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A comparison of sonographic estimation of fetal weight and obstetrically determined gestational age in the prediction of neonatal outcome for the very low–birth weight fetus

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A comparison of sonographic estimation of fetal weight and obstetrically determined gestational age in the prediction of neonatal outcome for the very low–birth weight fetus was conducted in a study population of 122 fetuses. With stepwise logistic regression, obstetric gestational age was found to be the best predictor of neonatal death, while sonographic estimated fetal weight did not add significantly to this prediction. However, both variables were important in the prediction of adverse neonatal outcome (neonatal death together with major neonatal complications of prematurity). (AM J OBSTET GYNECOL 1985;152:47-50.)

Key words: Very low–birth weight, sonogram, gestational age

The antenatal identification of the infant too small to benefit from maximal obstetric care continues to challenge the obstetric profession.[1-5] This clinical challenge is currently addressed by two methods used to predict outcome in the very low–birth weight fetus: obstetric gestational age assessment and antenatal estimation of fetal weight.[6] Obstetric gestational age assessment is the more widely used method and is best determined by the use of sonographically determined fetal biometry (biparietal diameter and femur length in conjunction with clinical assessment of gestational age).

The clinical estimation of fetal weight without sonographic corroboration is often markedly inaccurate.[2, 7] However, recently it has been shown by several investigators that sonographic estimation of fetal weight is possible, with a standard deviation of <10%.[8-11] Although sonographically determined estimated fetal weight has been used clinically to predict neonatal outcome for the very low–birth weight fetus, its predictive value relative to gestational age has not been examined.

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Table I. Neonatal death and adverse neonatal outcome as a function of estimated fetal weight

Estimated fetal weight (gm)	*n*	*Neonatal death*		*Adverse neonatal outcome*	
		n	*%*	*n*	*%*
501-600	7	4	57.1	7	100
601-800	16	8	50	16	100
801-1000	26	10	38.5	22	84.6
1001-1200	25	4	16	14	56
1201-1400	28	2	7.1	11	39.2
1401-1500	20	1	5	3	15
Total	122	29	23.8	73	59.8

Table II. Neonatal death and adverse neonatal outcome as a function of obstetric gestational age

Obstetric gestational age (wk)	*n*	*Neonatal death*		*Adverse neonatal outcome*	
		n	*%*	*n*	*%*
23-24	9	7	77.7	9	100
25-26	26	12	46.1	25	96.1
27-28	22	5	22.7	18	81.8
29-30	30	3	10	10	33.3
31-32	28	2	7.1	9	32.1
33-34	6	0	0	1	16.7
35-36	1	0	0	1	100
Total	122	29	23.8	73	59.8

The purpose of this article is to compare the ability of obstetric gestational age assessment and sonographic estimation of fetal weight to predict neonatal death and adverse neonatal outcome in the very low–birth weight fetus.

Material and methods

During the 5-year period from September 1, 1978, to September 1, 1983, 127 singleton live fetuses had sonographic estimations of fetal weight between 500 and 1500 gm at Yale–New Haven Medical Center and were delivered <3 days after the sonographic examination. The sonographic estimations of fetal weight were determined by the formula devised by Shepard et al.[9] Four cases in which severe anomalies (hydrops fetalis in three and renal agenesis in one) were identified at the time of the sonographic examination and one case in which neonatal follow-up information was not available were excluded, leaving a total study population of 122. Four cases of anomalies identified only after birth were not excluded from the study population. There were no stillbirths in this series.

Obstetric gestational age was determined by menstrual history and sonographic assessment of gestational age based on measurements of either biparietal diameter, femur length, or both. If gestational age as determined by last menstrual period and sonographic assessment of gestational age differed by <2 weeks, gestational age was based on the last menstrual period. If the discrepancy was >2 weeks or if the last menstrual period was unreliable (11 cases), gestational age was based entirely on sonographic assessment.

Neonatal gestational age was assessed according to the method of Ballard et al.,[12] but this assessment was not done in eight cases. Birth weight was measured in grams. A neonatal death was defined as a death that occurred ≤ 28 days after birth. An adverse neonatal outcome was considered to be a neonatal death or the presence of intraventricular hemorrhage documented by computed axial tomography or ultrasonography, prolonged ventilation or supplemental oxygen administration (≥ 30 days), retrolental fibroplasia, or necrotizing enterocolitis.

Stepwise logistic regression (Biomedical Data Package program LR) was used to evaluate the predictive ability of estimated fetal weight versus obstetric gestational age. The analysis was first performed with neonatal death used as the outcome variable and then repeated with adverse neonatal outcome used as the outcome variable. For a predictive variable to enter this logistic regression model, its association with the outcome variable had to be significant at least at $p \leq 0.10$.

Subsequently additional stepwise logistic regressions were performed to evaluate if other variables (maternal age, sex of infant, race, medical complication of pregnancy, obstetric complication other than prematurity, antenatal suspicion of intrauterine growth retardation based on sonographic parameters, suspicion of fetal distress based on bioelectric or biochemical parameters, place where sonography was performed [perinatal ultrasound unit versus labor and delivery suite], fetal presentation, delivery method, anomalies diagnosed after birth, and intrauterine growth retardation diagnosed after birth[13]) would add significantly to the predictive abilities of the aforementioned models. In addition, these analyses were repeated with the four postnatally diagnosed anomalies excluded.

Results

In the study population, the mean estimated fetal weight was 1077 gm with an SD of 282 gm, while the mean birth weight was 1144 gm with an SD of 321 gm. The correlation coefficient for the relationship between estimated fetal weight and birth weight was 0.83. The mean obstetric gestational age was 28.7 weeks with an SD of 2.7 weeks, while the mean neonatal gestational age was 30.3 weeks with an SD of 2.4 weeks. The correlation coefficient for the relationship between obstetric gestational age and neonatal gestational age was 0.66.

Table III. Stepwise logistic regression analysis comparing obstetric gestational age and estimated fetal weight in prediction of neonatal death and adverse neonatal outcome

Outcome parameter	*Predictive parameter*	*Regression coefficient*	*SE*	*Z test*	*Goodness-of-fit test*
Neonatal death	Obstetric gestational age (wk)	−0.47000	0.10400	−4.52 $p < 0.0001$	$\chi^2 = 3.08$; 6 degrees of freedom $p = 0.80$
	Estimated fetal weight (gm)	−0.00166*	0.00144*	−1.16* $p > 0.10$	
Adverse neonatal outcome	Obstetric gestational age (wk)	−0.33000	0.12800	−2.58 $p = 0.01$	$\chi^2 = 2.52$; 7 degrees of freedom $p = 0.93$
	Estimated fetal weight (gm)	−0.00466	0.00127	−3.66 $p = 0.0003$	

*Because $p > 0.10$, estimated fetal weight did not enter in the stepwise logistic regression. Results shown are those obtained when the variable estimated fetal weight was forced into the model.

There were 57 (46.7%) male infants and 65 (53.3%) female infants. Sixty-nine (56.6%) of the patients were white and 53 (43.4%) were nonwhite. Medical complications occurred in 23 (18.9%) of the cases and obstetric complications other than prematurity occurred in 74 (60.7%). Fetal distress was suspected in 33 (27.0%) of the cases and fetal intrauterine growth retardation in 31 (25.4%). In 30 (24.6%) of the cases, the sonograms were obtained in the perinatal ultrasound unit and in 92 (75.4%), the sonograms were obtained in the labor and delivery suite. There were 51 (41.8%) spontaneous vaginal deliveries, 14 (11.5%) low-forceps deliveries, two (1.6%) midforceps deliveries, and 55 (45.1%) cesarean sections. Four (3.2%) anomalies were diagnosed after birth and intrauterine growth retardation was found after birth in 42 (33.9%) cases.

Neonatal death occurred in 29 (23.8%) infants. Of the survivors, 24 (25.8%) had intraventricular hemorrhage, 16 (17.2%) had retrolental fibroplasia, six (6.5%) had necrotizing enterocolitis, and 17 (18.3%) required prolonged ventilation and/or oxygen administration. In the total study population, 73 (59.8%) had an adverse neonatal outcome. Tables I and II describe the frequency of neonatal death and adverse neonatal outcome as functions of estimated fetal weight (Table I) and obstetric gestational age (Table II).

When obstetric gestational age and sonographically determined estimated fetal weight were evaluated individually, each was found to be a highly significant predictor of both neonatal death and neonatal adverse outcome ($p < 0.0001$).

The results of stepwise logistic regression analysis comparing obstetric gestational age and estimated weight in the prediction of neonatal death and adverse outcome are summarized in Table III. In comparing the ability of estimated fetal weight and obstetric gestational age to predict neonatal death, obstetric gestational age entered the model ($p < 0.0001$) while estimated fetal weight did not ($p > 0.10$). However, in the antenatal prediction of an adverse neonatal outcome, both estimated fetal weight and obstetric gestational age were significant ($p = 0.0003$ and $p = 0.01$, respectively). As evidenced by the χ^2 goodness-of-fit test, both models fit the data adequately ($p > 0.10$).

When the other potential predictors were included in the analysis, none were found to enter either model. When the comparisons were repeated with the exclusion of postnatally diagnosed anomalies, the results remained unchanged.

Comment

When the obstetric gestational age and estimated fetal weight variables were tested individually, each was found to be a highly significant predictor of neonatal outcome. However, the more important clinical issue is the comparison of the predictive abilities of gestational age and weight variables. Stepwise logistic regression is a useful statistical method for such analysis. In this method, the most predictive variable enters the model first and other variables enter only if they provide a significant additional contribution to the prediction of the particular outcome. When neonatal death was used as the outcome variable, our results indicated that obstetric gestational age was the best predictor of outcome and sonographic estimation of fetal weight was of no additional predictive value.

However, we decided that neonatal death was too restrictive a variable when the outcome for the very low–birth weight infants was analyzed. Therefore adverse neonatal outcome was also examined as an outcome variable in which not only neonatal death but also the major complications of prematurity were included. However, it should be remembered that an adverse neonatal outcome does not necessarily predict an adverse outcome in later life. Both obstetric gestational age and estimated fetal weight added significantly to the prediction of adverse neonatal outcome.

Analysis was also performed to assess the predictive abilities of selected sociodemographic and medicoobstetric variables in addition to the measures of gestational age and growth. The fact that no other variable entered the models demonstrates that gestational age and weight variables were the important predictors of neonatal outcome in our data set. It is possible that in a larger study population some of the additional variables (for instance, fetal distress) would be important additional predictors of neonatal outcome.

In conclusion, the results of our study suggest that estimated fetal weight and obstetric gestational age are the most valuable predictors of neonatal outcome in the very low–birth weight fetus. Results of recent studies have suggested that birth weight is superior to gestational age assessment as a predictor of neonatal death.[15,16] Inaccuracies inherent in sonographically estimated weight determination may explain why our results do not support this conclusion. However, our findings do indicate that estimated fetal weight is a valuable predictor of adverse neonatal outcome when used both alone and in conjunction with obstetric gestational age. Unfortunately, because our relatively small study group may not have been representative of the general population, it was not possible to generate clinically useful nomograms to predict outcome based on antenatal gestational age assessment and sonographic estimated fetal weight, as are currently available for neonatal gestational age and birth weight.[16,17]

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1. Wren BG, Brown LB, Routledge DA: Differential clinical response to oestrogens after menopause. *Med J Aust* 2:329-332, 1982.

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WARNING:

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. OGEN SHOULD NOT BE USED DURING PREGNANCY.

According to some investigators, the use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. Studies have reported that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] In one of these studies, this risk was estimated as not greater than 4 per 1000 exposures.[7] Furthermore, there are reports that a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these reported changes are histologically benign, the investigators have not determined whether they are precursors of adenocarcinoma.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies in the offspring, including heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. OGEN has not been studied for these uses, and therefore should not be used during pregnancy. There is no evidence from well controlled studies that progestogens are effective for these uses.

If OGEN (estropipate tablets) is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the question of continuation of the pregnancy should be addressed.

INDICATIONS
OGEN (estropipate tablets) is indicated for the treatment of estrogen deficiency associated with:

1. Moderate to severe *vasomotor* symptoms of menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.

OGEN (ESTROPIPATE TABLETS) HAS NOT BEEN TESTED FOR EFFICACY FOR ANY PURPOSE DURING PREGNANCY. SINCE ITS EFFECT UPON THE FETUS IS UNKNOWN, IT CANNOT BE RECOMMENDED FOR ANY CONDITION DURING PREGNANCY (SEE BOXED WARNING).

CONTRAINDICATIONS
OGEN should not be used in women with any of the following conditions:

1. Known or suspected cancer of the breast.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (See Boxed Warning).
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use.

WARNINGS
1. *Induction of malignant neoplasms.* Long-term continuous administration of natural and synthetic estrogens in certain animal species has been reported by some investigators to increase the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning).

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent long-term followup of a single physician's practice has raised this possibility.[18] Therefore, caution should be exercised when administering estrogens to women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. Careful breast examinations should be performed periodically.

2. *Gall bladder disease.* A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens,[17] similar to the 2-fold increase previously noted in users of oral contraceptives.[19,22] In the case of oral contraceptives, the increased risk appeared after two years of use.[22]

3. *Effects similar to those caused by estrogen-progestogen oral contraceptives.* There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat postpartum breast engorgement would be more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in women receiving estrogens for postpartum breast engorgement.[20,21]

a. *Thromboembolic disease.* It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[22-29] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.[30,31] An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives.[32,33] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism; it should also be discontinued during periods of prolonged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found[17,34] this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk. Therefore estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

b. *Hepatic adenoma.* Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[36-38] Although benign, and rare, these may rupture and cause death through intraabdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[37] The relationship of this malignancy to these drugs is not known at this time.

c. *Elevated blood pressure.* Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with use of estrogens in the menopause[39] and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. *Glucose tolerance.* A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

4. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS
A. General Precautions.

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

2. Fluid retention — Estrogens may cause some degree of fluid retention. Therefore, patients with conditions such as epilepsy, migraine, and cardiac or renal dysfunction, which might be influenced by this factor, require careful observation.

3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression.[22] Although it is not clear whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size during estrogen use.

6. The pathologist should be advised of the patient's use of estrogen therapy when relevant specimens are submitted.

7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen.

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

B. Information for the Patient. See text of Patient Package Insert which appears after PHYSICIAN REFERENCES.

C. OGEN (estropipate tablets) cannott be recommended for use during pregnancy. See Contraindications and Boxed Warning.

D. Nursing Mothers. Estrogens have been reported to be excreted in human breast milk.

ADVERSE REACTIONS
(See Warnings regarding reports of possible induction of neoplasia, unknown effects upon the fetus, increased incidence of gall bladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

1. *Genitourinary system.*
Breakthrough bleeding, spotting, change in menstrual flow.
Dysmenorrhea.
Premenstrual-like syndrome.
Amenorrhea during and after treatment.
Increase in size of uterine fibromyomata.
Vaginal candidiasis.
Change in cervical eversion and in degree of cervical secretion.
Cystitis-like syndrome.

2. *Breast.*
Tenderness, enlargement, secretion.

3. *Gastrointestinal.*
Nausea, vomiting.
Abdominal cramps, bloating.
Cholestatic jaundice.

4. *Skin.*
Chloasma or melasma which may persist when drug is discontinued.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Loss of scalp hair.
Hirsutism.

5. *Eyes.*
Steepening of corneal curvature.
Intolerance to contact lenses.

6. *CNS.*
Headache, migraine, dizziness.
Mental depression.
Chorea.

7. *Miscellaneous.*
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria.
Edema.
Changes in libido.

ACUTE OVERDOSAGE
Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that serious ill effects do not occur. Overdosage of estrogen may cause nausea and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION
1. *Given cyclically for short-term use:*

For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., 3 weeks on and 1 week off).

Attempts to discontinue or taper medication should be made at 3 to 6 month intervals.

The usual dosage range is one OGEN .625 (estropipate) Tablet to one OGEN 5 Tablet per day.

2. *Given cyclically:*

Female hypogonadism. Female castration. Primary ovarian failure. The lowest dose that will control symptoms should be chosen. A daily dose of one OGEN 1.25 Tablet to three OGEN 2.5 Tablets may be given for the first three weeks of a theoretical cycle, followed by a rest period of eight to ten days. The same schedule is repeated if bleeding does not occur by the end of the rest period. The duration of cyclic estrogen therapy necessary to produce withdrawal bleeding will vary according to the responsiveness of the endometrium. If satisfactory withdrawal bleeding does not occur, an oral progestogen may be given in addition to estrogen during the third week of the cycle.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED
OGEN (estropipate tablets, USP) is supplied as OGEN .625 (0.75 mg estropipate), yellow tablets, **NDC** 0074-3943-04; OGEN 1.25 (1.5 mg estropipate), peach-colored tablets, **NDC** 0074-3946-04; OGEN 2.5 (3 mg estropipate), blue tablets, **NDC** 0074-3951-04; and OGEN 5 (6 mg estropipate), light green tablets, **NDC** 0074-3958-13. Tablets of all four dosage levels are standardized to provide uniform estrone activity and are grooved (Divide-Tab®) to provide dosage flexibility. All tablet sizes of OGEN are available in bottles of 100.

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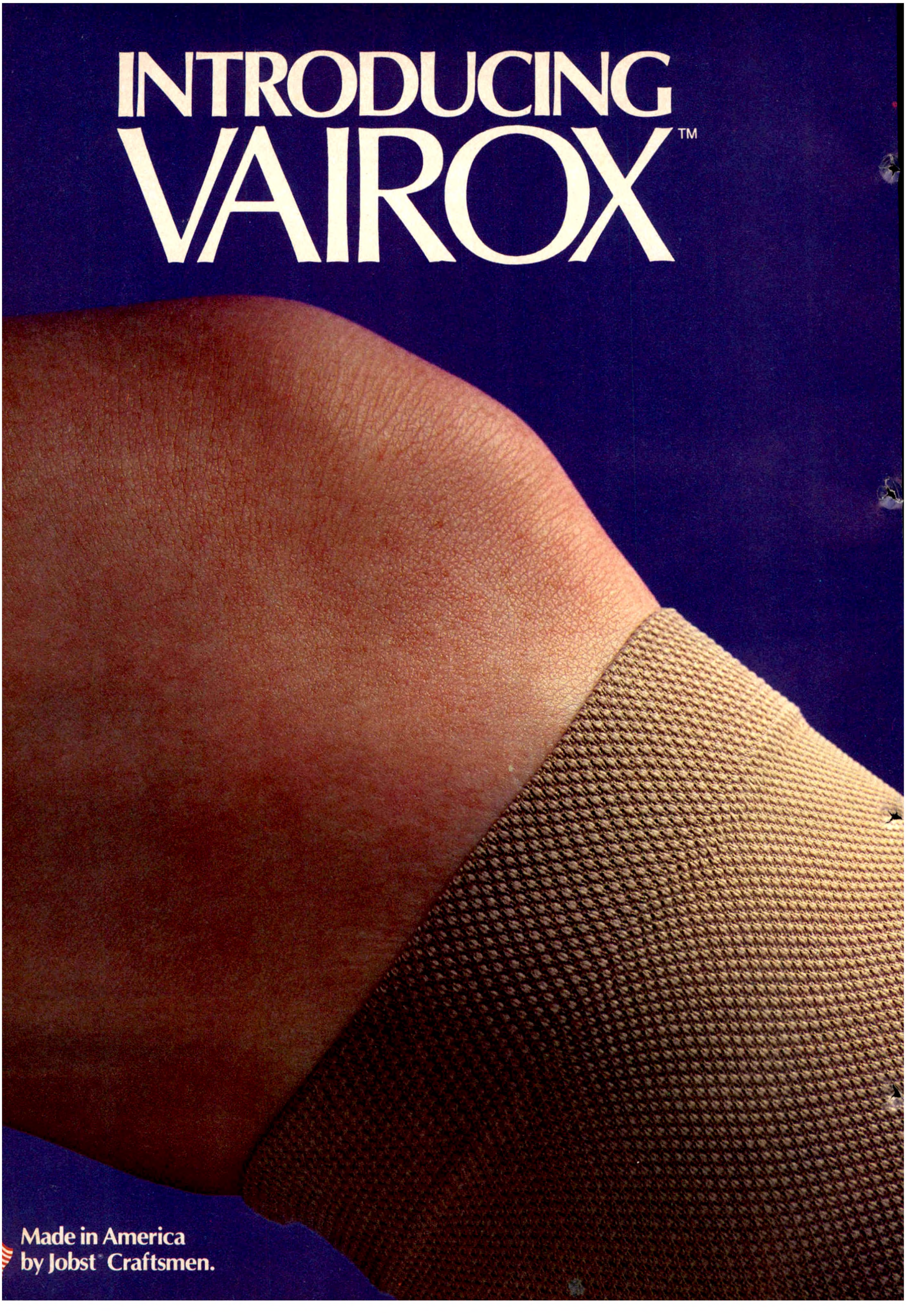
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Evaluation of gas-liquid chromatography for the rapid diagnosis of amniotic fluid infection: A preliminary report

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Gas-liquid chromatography has been proposed as a possible tool in the rapid diagnosis of amniotic fluid infections. The analysis is based on the identification of specific organic acids derived from bacterial metabolism when organisms are present within the amniotic fluid. We retrospectively subjected 69 samples of amniotic fluid which had been obtained by transabdominal amniocentesis to analysis by gas-liquid chromatography. Forty-seven samples were derived from patients who either were in premature labor or had premature rupture of membranes with associated premature labor. Twenty-two specimens which served as a comparison group were obtained from patients who underwent amniocentesis for assessment of fetal maturity. The results obtained from chromatographic analysis are presented, and the possible applications of this technique to the clinical situation are discussed. (Am J Obstet Gynecol 1985;152:51-6.)

Key words: Amniotic fluid, gas-liquid chromatography, bacterial infection

Unrecognized bacterial colonization of the amniotic fluid was first proposed as a possible cause of premature labor by Bobitt and Ledger.[1] Since their report, other investigators have demonstrated the presence of bacteria in the amniotic fluid of 21% to 26% of patients with premature labor[2-4] and 35% of patients with premature rupture of membranes.[5] The identification of such infections are important since preterm infants born to mothers with amniotic fluid infection are at greater risk of neonatal morbidity and mortality.[6]

Current trends in obstetric practice have included the widespread use of tocolytic agents to arrest premature labor in an attempt to prolong intrauterine development. The identification of significant intra-amniotic bacterial colonization would contraindicate such efforts to delay delivery.[7] Clinical signs and symptoms of infection generally represent late findings. Even culture results often require 24 to 48 hours, and this delay could potentially have adverse effects on the pregnancy outcome. To more rapidly identify the presence of subclinical infections, various tests have been examined, such as amniotic fluid leukocyte count[4] and Gram stain,[4] quantitative microbial cultures of amniotic fluid,[2-5] measurement of C-reactive protein in maternal serum,[8] and elevations of amniotic fluid lactic dehydrogenase.[2] For each of these tests, studies have been reported which did not find close correlations with clinical infections.[5, 9-11]

In 1980, Spiegel et al.[12] adapted the use of gas-liquid chromatography to the female genital tract for the identification of short-chained organic acids which are specific metabolites of microorganisms. Gravett et al.[13] first applied this technique to the evaluation of amniotic fluid for clinical infection. They reported that an abnormal gas-liquid chromatographic pattern that consisted of acetate, propionate, or butyrate together with succinate was 94% sensitive and 95% specific for amniotic fluid infection. To evaluate the usefulness of gas-liquid chromatography for the rapid identification of amniotic fluid infection in our population, we retrospectively examined samples of amniotic fluid from 47 women who had been seen in consultation for premature labor or premature rupture of membranes with associated premature labor.

Material and methods

Study population. The study population consisted of 69 patients who were seen at The Perinatal Center of Abbott-Northwestern Hospital, Minneapolis, between November, 1982, and July, 1983. Forty-seven of the patients, who represented the study cases, presented with either premature labor (32) or premature rupture of membranes with associated premature labor (15). Fifteen of these patients (32%) manifested signs and symptoms of clinical infection at the time the amniocentesis was performed. The diagnosis of clinical in-

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Table I. Indication for amniocentesis in the comparison group

Fetal hydrops	4
Fetal anomalies on ultrasound	3
Repeat cesarean section	3
Pregnancy-induced hypertension	3
Maternal diabetes mellitus	3
Suspected intrauterine growth retardation	2
Positive oxytocin challenge test	2
Placenta previa	2

fection was based on the criteria outlined by Gibbs et al.[7] Amnionitis was diagnosed if the patient had two or more of the following: a temperature greater than 38.0° C, uterine tenderness, foul-smelling amniotic fluid, or a peripheral leukocytosis. Other sources of infection had been excluded. Comparison samples of fluid were obtained from 22 patients who underwent amniocentesis to assess fetal pulmonary maturity. None of the patients in the comparison group were in premature labor, had rupture of membranes, or manifested any signs or symptoms of amnionitis. The indications for amniocentesis in the comparison group are listed in Table I.

Evaluation of amniotic fluid. All samples of amniotic fluid were collected by transabdominal amniocentesis after informed consent had been obtained from the patients. After aspiration, a portion of the fluid was transported in a capped syringe for immediate culturing. In the laboratory, a smear was prepared for Gram stain, and fluid was inoculated onto blood agar (Columbia-based agar plus 5% defibrinated sheep's blood), MacConkey plates, chocolate agar with Isovitalex (Gibco, Madison, WI), and colistin-naladixic acid blood agar for aerobic isolation. Selective media were not used for the isolation of group B β-hemolytic streptococci. Prereduced chopped-meat carbohydrate broth (Gibco, Madison, WI) and sheep's blood Columbia-based agar were inoculated and maintained in Gas Paks to isolate anaerobes. Anaerobes were identified by means of techniques described in the Virginia Polytechnic Institute *Anaerobe Laboratory Manual.*[14] The remaining amniotic fluid was preserved in a frozen state (−20° C) prior to analysis by gas-liquid chromatography. When thawed, specimens were prepared for gas-liquid chromatographic analysis by acidification and extraction according to the technique described by Spiegel et al.[12] A chromatograph equipped with a flame ionization detector (5840 A-Hewlett-Packard, Avondale, PA) was used to analyze the samples. A 2 μl sample was injected onto a column packed with SP-1000 (Supelco, Bellefonte, PA) and helium carrier gas, 20 ml/min. (This varied from the method of Spiegel et al. in that nitrogen was the carrier gas originally described.) The height of the peaks was measured and recorded in millimeters.

Statistical analysis. Data were analyzed by Student's *t* test or χ^2 with Yate's correction wherever appropriate.

Results

Study population (Table II). Patients with premature labor or premature rupture of membranes did not differ from patients in the comparison group in regard to age, source of third-party payment, or method of delivery. However, patients in the study group were more likely to be single than either married or divorced ($P = 0.05$), and their gestational age at the time of amniocentesis was significantly less than that of the comparison group ($p < 0.0001$).

Microbiologic findings. Bacteria were isolated from the amniotic fluid of nine of 47 (19%) study patients. None of the comparison samples of fluid was found to contain organisms. At the time of amniocentesis, six of the nine patients with positive cultures had signs of clinical infection. Anaerobic organisms were recovered from only two of the nine samples of fluid (22%). Signs and symptoms of clinical infection were present in a total of 15 patients at the time of amniocentesis. In seven of these 15 patients, Gram stain and culture of the amniotic fluid were negative, as was the vaginal culture for group B β-hemolytic streptococci. Table III summarizes laboratory findings in 28 of 47 study patients. The other 19 patients manifested no abnormalities on laboratory examinations.

Positive Gram stains were found in five cases. All 5 of these samples of amniotic fluid also yielded organisms on culture. This finding supports the work of Miller et al.[4] who found that the Gram stain was highly predictive of a positive culture. One of the patients with a positive Gram stain and amniotic fluid culture positive for *Lactobacillus* did not have signs or symptoms of clinical infection, but she was in premature labor at 32 weeks' gestation. A urinary tract infection due to *Escherichia coli* was later identified. After treatment with ampicillin, the premature labor remitted and the pregnancy progressed to 38 weeks, at which time the patient was delivered of a normal child with no evidence of infection.

Vaginal cultures to identify group B β-hemolytic streptococci were obtained on all patients with either premature rupture of the membranes or premature labor. Group B β-hemolytic streptococci was isolated from nine of 47 (19%) of the study patients but from none of 11 comparison patients in whom vaginal cultures were obtained. This difference was not significant, although the number in the comparison group was small. In six of these nine, other organisms were

Table II. Relationships between the group with premature labor and premature rupture of membranes and the comparison group

	Comparison group (n = 22)	*Premature labor and premature rupture of membranes group (n = 47)*	
Age, yr (mean)	28	26	NS
Marital status			
Married/divorced	22	35	
Single	–	12	p = 0.05
Socioeconomic status			
Insured	21	41	
Public assistance	1	6	NS
Mean gestational age at amniocentesis (wk)	35	31	p < 0.0001
Method of delivery*			
Vaginal	6	25†	
Cesarean section	13	19	NS

*Three control patients and seven study patients were discharged prior to delivery, and information concerning outcome was unavailable. All delivered after 37 weeks' gestation.

†Forty-four infants were available for follow-up in the case group—37 singletons, two twins, and one triplet.

isolated from amniotic fluid cultures. It is noteworthy that group B β-hemolytic streptococci was not isolated from any of the specimens of amniotic fluid.

Chromatographic profiles. All samples of amniotic fluid, whether from the study patients or the comparison patients, contained lactate. The mean lactate peak (±SD) was 34.7 ± 9.7 in the comparison group and 42.8 ± 10.4 ($p < 0.01$) in the group with premature labor or premature rupture of membranes with associated premature labor. Thus, the lactate peak was significantly more likely to be higher in the study patients than in the comparison patients. This finding was not unexpected, since all patients in the study group were in premature labor. During labor, lactate would be expected to accumulate in the maternal circulation, thus elevating the amniotic fluid lactate. Acetate was the next most commonly identified organic acid. Peak heights ≥ 1 mm were found in seven of 22 comparison patients and in 16 of 47 study patients ($p > 0.05$, NS). There was no significant difference between the heights of the acetate peaks in the study group (1.06 ± 0.9) and those in the comparison group (0.82 ± 0.47). Bacteria were recovered from six patients in whom acetate was detected. This finding differs from that of Gravett et al.,[13] who recovered bacteria from all samples of fluid in which acetate was detected.

A succinate peak was present in 12 of the 47 study patients and in two of the 22 comparison patients. There was no significant difference between the heights of the succinate peaks in the study group (0.79 ± 0.4) and those in the comparison group (0.5). However, only in the study group were peak heights greater than trace recorded (four patients). The amniotic fluid of the two patients in the comparison group that contained trace succinate also yielded lactate and acetate. Both samples of fluid were obtained from pregnancies in which the infant was severely hydropic. Neither patient was in premature labor, and organisms were not isolated from the fluid of either. The significance of this observation is not immediately evident, but the possibility that it is directly related to the clinical condition of the fetus would not be expected, because of the proposed bacterial origin of these organic acids.

Organisms were recovered from nine samples of amniotic fluid in this series, and three had acetate and/or succinate peaks of ≥1 mm. Of the other six cases in which organisms were recovered from amniotic fluid, the organism recovered in four would not be expected to produce an organic acid (*Candida albicans, Lactobacillus*). The two patients with *Gardnerella vaginalis* and *Bacteroides* sp. would be expected to have organic acids present. We are unable to explain the failure to identify peaks other than lactate in these specimens of fluid.

Peaks of organic acids other than lactate, acetate, or succinate were found in eight specimens of amniotic fluid, (five study patients and three comparison patients). The acids identified were pyruvate, oxalate, and caproate. The significance of these peaks is not immediately evident. They were not reported by Gravett et al.[13] Interestingly, pyruvate was found only in the group of patients with either premature labor or premature rupture of membranes associated with labor. The amniotic fluid of two of the four study patients in whom pyruvate was present yielded organisms on culture. However, positive culture did not correlate with the height of the organic acid peak. A fifth specimen of fluid contained oxalate. Of the three comparison samples of fluid, two contained oxalate, and the third had caproate identified in it.

No specific gas-liquid chromatographic pattern was

Table III. Microbiologic and gas-liquid chromatographic profiles in patients with premature labor or premature rupture of membranes*

Gram	*Culture*	*Vaginal† streptococci*	*Clinical infection*	*Microbiologic findings*	*Lactate*	*Acetate*	*Succinate*
N	+	N	+	4+ *Streptococcus pneumoniae*	35	1.5	
+	+	+	+	*Candida albicans*	49	Trace	
+	+	+	+	*Candida albicans*	50	Trace	
+	+	N	+	*Candida albicans*	58	Trace	
+	+	N	+	*Pseudomonas* aeruginosa	67	1.0	1.0
N	+	+	+	*Gardnerella* vaginalis (broth), *Bacteroides* Sp.	65		
N	N	+	+		45	Trace	
N	N	N	+		47	Trace	
N	N	N	+		42	1.0	
N	N	N	+		34	4	Trace
N	N	N	+		44	Trace	Trace
N	N	N	+		34		
N	N	+	+		25		
N	N	+	+		35	1.0	
N	N	N	+		42	2.0	
N	+	+	N	*Gardnerella* vaginalis (broth), *Bacteroides* sp.	34		
+	+	N	N	4+ *Lactobacillus*	32		
N	+	N	N	2+ *Staphylococcus epidermidis*	43	1.0	
N	N	N	N		51	1.0	1.0
N	N	N	N		57	Trace	Trace
N	N	N	N		46	1.5	1.5
N	N	N	N		52	1.5	1.5
N	N	N	N		46	1.5	Trace
N	N	N	N		48	Trace	Trace
N	N	N	N		49	Trace	Trace
N	N	+	N		42	Trace	
N	N	+	N		48	Trace	
N	N	+	N		46	Trace	

N = Results of the study were negative. + = Results of the study were positive.

*Twenty-eight of 47 cases are presented. In the other 19 cases, no microbiologic, laboratory, or chromatographic abnormalities were found.

†Vaginal cultures were obtained on all patients in premature labor or with PROM to screen for group B-β-hemolytic streptococci.

identified which was consistently associated with premature labor or premature rupture of membranes with associated premature labor. No consistent correlation was found between the heights of the organic acid peaks and either premature labor, premature rupture of membranes, the presence of clinical infection, or positive cultures of amniotic fluid. The data obtained did not permit a discrete definition of an abnormal gas-liquid chromatographic pattern, because of the few specimens with measurable acetate or succinate peaks.

Comment

It has been estimated that 20% or more of the cases of premature labor and PROM may be due to occult infection of amniotic fluid.[1-4] The current obstetric management favors a conservative approach to these clinical situations, with the use of tocolytic agents to delay delivery in selected cases. Methods have been sought to rapidly identify patients with possible subclinical infection of amniotic fluid since they could be adversely affected by delay of delivery.[7] Current screening tests for amniotic fluid infection include the presence of bacteria on Gram stain,[4] leukocytes in amniotic fluid,[4] maternal serum C-reactive protein,[8] and elevated levels of lactic dehydrogenase.[2] For each of these tests, studies have been reported which did not find a correlation with clinical infection.[5, 9-11]

In 1982, Gravett et al.[13] reported on the use of gas-liquid chromatography for predicting the presence of amniotic fluid infection. They stated that gas-liquid chromatography analysis was "94% sensitive and 95% specific for amniotic fluid infection, and correlated with the growth of bacteria in amniotic fluid."[13] In their study, the presence of either acetate, propionate, or butyrate in association with succinate correlated with amniotic fluid infection. Their hypothesis is that organic acids other than lactate are derived from bacterial metabolism when organisms are present within amniotic fluid and thus can serve as a marker for amniotic fluid infections. To evaluate the clinical usefulness of this technique in our patient population, we undertook a preliminary retrospective study of 69 specimens of amniotic fluid, 47 obtained from patients either in premature labor or with premature rupture of membranes associated with premature labor and 22 derived from patients without any signs or symptoms of either premature labor or clinical infection. All specimens of fluid had been obtained by transabdominal amniocentesis prior to the study and were maintained in a frozen state (−20° C) until gas-liquid chromatography analysis.

The results of this study differ from the findings of Gravett et al.[13] Eighteen patients in this study had either a positive amniotic fluid culture or manifested signs of clinical infection, or both. Only seven of the 18 specimens of fluid contained organic acid peaks other than lactate. In contrast, amniotic fluid from 11 of the other 51 patients without either clinical infection or positive amniotic fluid culture contained organic acids other than lactate ($p > 0.05$, NS). Thus, we were unable to demonstrate a statistically significant association between the presence of organic acids other than lactate and either clinical infection or positive amniotic fluid culture in a group of patients who presented with premature labor and/or premature rupture of the membranes. In both studies, lactate peaks were significantly higher in study patients than in comparison patients. However, predictive values based on the heights of the organic acid peaks could not be identified in this study. Our differing results cannot be immediately explained. Possibly, the composition of organic acids might differ among patient populations because of either geography or socioeconomic status. Our patients represent a private practice referral population located in the upper Midwest. Only seven of 69 (10%) were receiving medical assistance. The remainder of the patients had either private insurance or were participants in a health maintenance organization. The possibility that long-term (up to 10 months) freezing may have affected the gas-liquid chromatography results must also be considered. Specimens were stored at −20° C in plastic vials. Acidification was undertaken after freezing. Very possibly, organic acids could either attach to or leach out of the plastic vial or otherwise volatilize and be lost in the freeze-thaw process. However, the possible effects of freezing do not explain why 11 of the 14 specimens of amniotic fluid in which succinate was present on analysis after freezing were negative for growth when cultured. All cultures were performed at the time the amniocentesis was done, prior to freezing. A limitation of the present study was that cultures were not repeated at the time that gas-liquid chromatography was performed. Furthermore, it is possible that the concentration of organisms needed for culture identification was too small without special isolation media or enhancement techniques. Quantitative amniotic fluid culture and gas-liquid chromatography analysis are underway in our laboratory to ascertain the threshold concentration of organisms needed to consistently yield chromatographic peaks and positive cultures with the use of standard isolation techniques.

The heights of the chromatographic peaks in the report by Gravett et al.[13] were considerably higher than those obtained in the present study. This could reflect either a difference in study populations or a possible effect of freeze-thawing. Their work did not report the gestational ages of the study patients and comparison patients. However, since they state that there was no difference between the two groups, we must assume that they were closer to term. The effect that gestational age may have on the composition or concentration of these factors is unknown. Since these acids are believed to be derived from bacterial sources, we assume that gestational age does not affect their presence, but this has not been investigated.

The presence of a chromatographic succinate peak was highly correlated with infection in the group reported by Gravett et al.[13] In the present study, succinate was present in two of 22 (9%) comparison patients and in 10 of 47 (21%) study patients. This observation approached but did not reach significance ($0.5 > p > 0.1$). If the four isolates not expected to yield succinate are excluded, three of the other five isolates manifested succinate peaks. Even though the numbers are small, we think that the results are encouraging and warrant further investigation.

The modern use of tocolytic agents to delay delivery in selected cases of premature labor or premature rupture of membranes necessitates rapid methods for the detection of subclinical amniotic fluid infection. A direct assay of microbial metabolism should be preferable to indirect studies which depend on maternal or fetal response to the infecting agent(s). Recognizing the retrospective nature of this study, as well as the technical limitations discussed above, we think that this study does not disallow the possible application of this technique to the rapid evaluation of possible amniotic fluid infection in selected cases. The use of gas-liquid chromatography alone for the diagnosis of amniotic fluid infection cannot be recommended at this time. However, when combined either with currently available tests, microbiologic enhancement techniques, the presence of inhibitory factors in amniotic fluid, or other bacterial metabolic byproducts, this analysis could contribute to the clinician's ability to more rapidly diagnose amniotic fluid infection. We have undertaken, therefore, at our center, a prospective study of the usefulness of gas-liquid chromatography for the rapid detection of amniotic fluid infection associated with either premature labor or premature rupture of membranes with associated premature labor. This will help us to more accurately determine the possible use of gas-liquid chromatography for identifying amniotic fluid infection in our population.

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Maternal and fetal β-endorphin release in response to the stress of labor and delivery

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In order to clarify the stress effect of labor on maternal and neonatal plasma levels of β-endorphin, we measured this peptide in samples taken from 40 pregnant patients and their neonates at the time of normal vaginal delivery (n = 15), and at cesarean section performed either in early labor (n = 13) or prior to labor (n = 12). The mean (±SE) maternal plasma concentration of β-endorphin in the vaginal delivery group was 40.3 ± 5.6 fmol/ml, which was significantly higher than that in their neonates (21.3 ± 2.9 fmol/ml). In contrast, maternal levels of β-endorphin in the cesarean section groups (8.2 ± 1.2 and 8.5 ± fmol/ml) were significantly lower than those in their neonates (23.3 ± 5.6 and 15.6 ± 2.8 fmol/ml). Concentrations of β-endorphin in mothers delivered vaginally were also significantly higher than those in mothers delivered by cesarean section. However, there was no difference in mean cord levels of β-endorphin among the three groups. These findings indicate that (1) neither the presence or absence of labor affects fetal plasma β-endorphin secretion and (2) the stress of labor and delivery produces a marked increase in maternal release of β-endorphin. (AM J OBSTET GYNECOL 1985;152:56-9.)

Key words: β-Endorphin, labor, stress

β-Endorphin is a 31-residue opioid peptide formed by enzymatic cleavage of β-lipotropin, a split product from pro-opiomelanocortin, which is also the precursor of adrenocorticotropin (ACTH).[1] All of the abovementioned peptides are localized within the pituitary corticotrophs,[2] and the adenohypophysis is the major source of endorphins, particularly β-endorphin, that are found in peripheral blood during stress.[3] Guillemin

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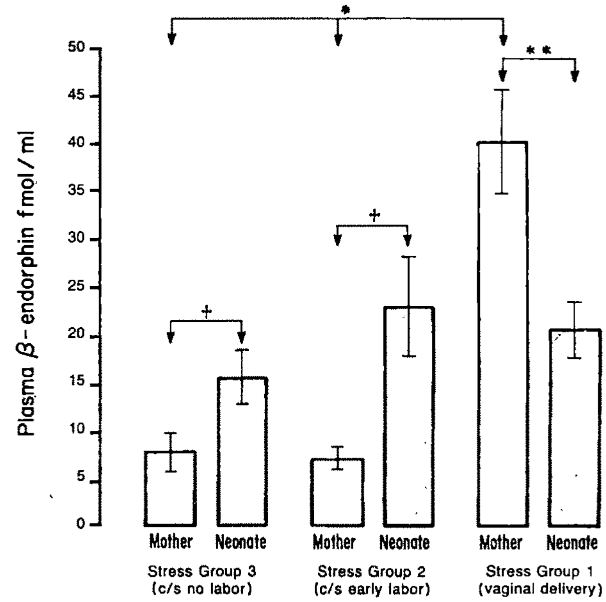

Fig. 1. Mean (±SE) concentrations of β-endorphin in maternal and neonatal plasma in the three different stress groups. (*$p < 0.001$; **$p < 0.01$; †$p < 0.05$). *c/s* = Cesarean section.

et al.[3] reported that in rats ACTH and β-endorphin are concomitantly secreted by the pituitary gland in response to acute stress, and hypophysectomy abolishes this response.

Since labor and delivery are considered to be states of extreme emotional and physical stress, the pro-opio melanocortin derivatives may be involved in the mechanisms of maternal and fetal adaptation to this stressful state. Csontos et al.[5] have already shown that maternal plasma levels of ACTH and β-endorphin are markedly elevated during labor, with the highest concentrations immediately after delivery. They also found high umbilical cord plasma levels of β-endorphin, but lower than maternal levels. No data have been published on the fetal plasma levels of β-endorphin in early labor. In an attempt to clarify further the role of β-endorphin, we measured this opioid in maternal and umbilical cord plasma at the time of vaginal delivery and at cesarean section in patients either in early labor or prior to labor.

Material and methods

The study involved 40 pregnant patients and their neonates, divided into three "stress" groups. Stress group 1 consisted of 15 mothers and their neonates who had an uneventful labor and normal vaginal delivery. Stress group 2 consisted of 13 mothers and their neonates who were delivered by cesarean section when they were in definite early labor (cervical dilatation <5 cm). The indications for their surgical delivery were previous cesarean section ($n = 11$) and high breech presentation in labor ($n = 2$). Stress group 3 consisted of 12 mothers and their neonates who were delivered by elective repeat ($n = 9$) or primary ($n = 3$) cesarean section in the absence of labor. All mothers in the three groups were healthy and had normal antepartum courses, except for two who had Class B diabetes and one who was chronically hypertensive in group 3. All of them were delivered between 35 and 41 weeks' gestation. None of the 40 mothers received any medication, including analgesics, prior to delivery or induction of anesthesia. Eight mothers from group 2 and eight from group 3 were delivered under general anesthesia, and the rest under epidural anesthesia.

All neonates in the three groups had 1-minute Apgar scores >7, except for two delivered by cesarean section (groups 2 and 3), who had scores of 6 and 8 and 6 and 9, respectively.

Blood was withdrawn from the mothers in 10 ml plastic syringes at 1 minute before the induction of anesthesia or at the time of vaginal delivery. Mixed umbilical cord blood (5 ml) was collected within 1 minute after the cord was clamped and cut. All collected samples of blood were placed into ice-chilled siliconized glass tubes that contained ethylenediaminetetraacetic acid and bacitracin. The specimens were centrifuged immediately thereafter for 30 minutes at 3,000 rpm at 4° C, and the supernatant plasma was transferred into chilled siliconized glass tubes, immediately frozen, and stored at −75° C until assayed.

β-Endorphin was extracted from plasma by affinity gel extraction method with the use of specific Sepharose adsorption particles and then measured by a highly specific radioimmunoassay (β-endorphin radioimmunoassay kit, Immunonuclear Corp., Stillwater, Minnesota). This radioimmunoassay method is based on a rabbit antibody with high sensitivity to β-endorphin. The antibody to β-endorphin cross-reacts 100% with human β-endorphin, (Des-Tyr') human β-endorphin, (2-me-Ala^{2}) β-endorphin, and N-acetyl β-endorphin. The antibody demonstrated 5% cross-reactivity with β-lipotropin (β-LPH), and no cross-reactivity with α-endorphin (β-LPH$^{61-76}$), γ-endorphin (β-LPH$^{61-77}$) (D-Ala^{2})- β- endorphin, dynorphin, α-neo-endorphin, leukine enkephalin, methionine enkephalin, ACTH$^{1-39}$, ACTH$^{1-24}$, α-melanocyte–stimulating hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, thyrotropin, vasopressin, and oxytocin.

Assays were performed in duplicate, and the results were averaged. The intra-assay and interassay coefficients of variation were 13.7% and 18.1%, respectively. Results were evaluated by analysis of variance and two-tailed Student's *t* test and corroborated by nonparametric procedures.

Results

The maternal and cord plasma concentrations of β-endorphin at the time of delivery in the three stress groups are shown in Fig. 1.

The mean ± SE plasma β-endorphin concentration measured at the time of delivery in 15 mothers delivered vaginally (stress group 1) was 40.3 ± 5.6 fmol/ml, which was significantly higher ($p < 0.01$) than the mean plasma β-endorphin concentration (21.3 ± 2.9 fmol/ml) of their neonates. In contrast, the mean plasma concentrations of β-endorphin in mothers delivered by cesarean section in early labor (stress group 2: 8.2 ± 1.2 fmol/ml), as well as those not in labor (stress group 3: 8.5 ± 1.9 fmol/ml) were significantly lower ($p < 0.05$) than those of their neonates (23.3 ± 5.6 and 15.6 ± 2.8 fmol/ml, respectively).

Comparison among mean maternal plasma levels of β-endorphin indicates that mothers delivered vaginally have values significantly higher ($p < 0.001$) than those of mothers delivered by cesarean section, whether in early labor or not. However, there was no difference in mean cord plasma concentrations of β-endorphin among the three groups.

Comment

This study was designed to assess maternal and umbilical cord plasma levels of β-endorphin in response to gradually increasing levels of stress (no labor, early labor, and full labor) and the possible relationship of maternal plasma concentration of β-endorphin to umbilical cord plasma level of β-endorphin. Our data indicate that there is no significant difference in the mean levels of umbilical cord plasma β-endorphin among the three stress groups. Also, there was no difference in the mean levels of β-endorphin in the maternal plasma during early labor (stress group 2) as compared to the state of no labor (stress group 3). However, there was a significant fivefold increase in the maternal plasma levels of β-endorphin after full labor (stress group 1).

A comparison of maternal and cord mean plasma levels of β-endorphin in each stress group separately revealed that in the no-labor and early labor groups the mean cord plasma levels of β-endorphin were significantly higher than the corresponding maternal levels. This relationship was reversed in stress group 1 (vaginal delivery), in which we observed maternal levels significantly higher than the corresponding cord plasma levels of β-endorphin.

Our results are in agreement with, and extend the findings of Csontos et al.,[5] who reported that maternal plasma β-endorphin at the time of vaginal delivery is significantly higher than the cord plasma levels of β-endorphin. Other investigators[4-7] did not find a difference between maternal and cord plasma levels of β-endorphin. However, those studies included a relatively small number of subjects, used a mixed population, and/or used an endorphin assay that was not very specific.

Interestingly, Wardlaw et al.[8] reported an inverse correlation between umbilical cord plasma levels of β-endorphin and pH and P_{O_2}, thus suggesting that the increased levels of β-endorphin were the result of fetal hypoxia and acidosis. Shaaban et al.[9] found significantly higher levels of β-endorphin in neonates with fetal distress, thus supporting the findings of Wardlaw et al. that fetal hypoxia elevates the levels of β-endorphin in cord plasma. Our finding that neither the presence or absence of labor nor the method of delivery affects fetal plasma levels of β-endorphin in the absence of fetal distress is in agreement with these findings.

The lack of correlation between the simultaneously measured maternal and cord plasma levels of β-endorphin in all three stress groups suggests that the maternal and fetal secretions of β-endorphin are independently regulated. It is well known that β-endorphin is secreted in response to acute stresses, such as pain and insulin-induced hypoglycemia, as well as administration of Pitressin and metyrapone. The increased circulating amounts of β-endorphin after stress are hypophyseal in origin.[3] The high concentrations of β-endorphin in maternal plasma at the time of delivery probably provide some degree of analgesia to the mother. They may also counteract the effects of the high levels of catecholamines on the cardiovascular system. The physiologic role and significance of β-endorphin present in the fetal circulation remains totally unknown. The finding that the stress of labor and delivery does not affect the fetal β-endorphin system tempts us to speculate that either pain is not a stimulus for the release of β-endorphin in the fetus, or the fetus does not suffer pain during labor.

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Methotrexate with citrovorum factor rescue in gestational trophoblastic disease

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Thirty-three patients with gestational trophoblastic disease treated with methotrexate alone and 68 similar patients treated with methotrexate and citrovorum factor rescue were analyzed. Both groups showed a comparable sustained biochemical remission rate. The group treated with methotrexate and citrovorum factor however showed a shorter interval to induction of remission ($p < 0.05$). Contrary to previous reports,[3, 5] the methotrexate and citrovorum factor regimen failed to protect the patients against the development of hepatic toxicity, the incidence of hepatic toxicity being significantly higher in the group treated with methotrexate and citrovorum factor. (AM J OBSTET GYNECOL 1985;152:59-62.)

Key words: Methotrexate, citrovorum, gestational trophoblastic disease

Prior to the introduction of methotrexate, results of the treatment of gestational trophoblastic tumors were poor.[1] Li et al.[2] were the first group to report the dramatic response of gestational trophoblastic tumors to methotrexate in 1956. Methotrexate exerts its antineoplastic effect mainly by the inhibition of the enzyme dihydrofolate reductase, thus blocking the conversion of dihydrofolic acid to tetrahydrofolic acid (folinic acid) and by the inhibition of both purine and thymine synthesis. The use of calcium leucovorum (folinic acid) following the administration of methotrexate allows the use of higher doses of methotrexate without additional toxicity.[3, 4]

Since 1976, methotrexate with citrovorum factor rescue has been used in the Department of Gynaecology, University of Hong Kong, in the treatment of gestational trophoblastic disease. The present report concerns our experience in the use of methotrexate with folinic acid and methotrexate alone in the treatment of gestational trophoblastic disease in Hong Kong.

Methods

Between July, 1972, and July, 1980, all patients with low-risk gestational trophoblastic disease treated in the Department of Obstetrics and Gynaecology, University of Hong Kong, were analyzed. Patients with persistent or metastatic gestational trophoblastic disease were divided into low-, medium-, and high-risk groups according to various risk factors as shown in Table I. The patient was defined as low risk if the score was <4, moderate risk if the score was 4 to 6, and high risk if the score was >6.

All patients were treated on an inpatient basis. The criteria for commencing chemotherapy included stationary or rising human chorionic gonadotropin (hCG) titers or a histologic diagnosis of choriocarcinoma. When the hCG titers plateaued, the period of observation was 4 weeks before the commencement of chemotherapy.

Before July, 1976, the treatment consisted of methotrexate only and 33 patients received such treatment. After July, 1976, our treatment for gestational trophoblastic disease was changed from methotrexate alone to a methotrexate–folinic acid regimen and 68 patients receiving the latter regimen were assessed. The general characteristics of these two groups of patients are comparable, as shown in Table II.

Pretreatment evaluation. Pretreatment investiga-

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Table I. Prognostic score in gestational trophoblastic disease

Parameter	*Score* *0*	*1*	*2*	*3*
1. Antecedent pregnancy	Hydatidiform mole	Nonmolar abortion	Term pregnancy	—
2. Interval in months between end of antecedent pregnancy and initial therapy*	<3	3-6	7-12	>12
3. hCG value at time of initial therapy†	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$
4 Largest tumor (cm)‡	<2	—	2-5	>5
5. Site of metastases	—	—	Gastrointestinal tract, kidney, spleen	Brain, liver
6. No. of metastases identified	—	1-4	4-8	>8
7. Previous chemotherapy§	—	—	Failed prophylactic chemotherapy	Failed therapeutic chemotherapy

*When the antecedent pregnancy cannot be identified, use interval in months from onset of symptoms.

†Use serum hCG β-subunit concentration (international units per liter or milli-international units per milliliter) when available. If urinary hCG is used, calculate as hCG, international units per 12 hours (half of daily excretion rate).

‡Take mean of largest and smallest diameters of biggest measurable tumor.

§Prophylactic chemotherapy is therapy starting within 3 weeks of primary evacuation of hydatidiform mole. Therapeutic chemotherapy is any prior chemotherapy for established trophoblastic tumor.

Table II. General characteristics of patients treated with methotrexate alone and methotrexate–folinic acid

	Methotrexate group (33 patients)	*Methotrexate–folinic acid group (68 patients)*
Age (yr)	26.5 (range 21-47)	32.1 (range 15-49)
Antecedent molar pregnancy	100%	100%
Interval from molar pregnancy to chemotherapy (mo)	2.6 (range 1-4)	2.1 (range 1-4)
Prior chemotherapy	None	None
Lung metastases (No.)	9	12
Vaginal metastases (No.)	2	2
Broad ligament metastases (No.)	–	1
Invasive mole (No.)	4	2
Choriocarcinoma (No.)	2	6
Hysterectomy (No.)	6	3

tions included a thorough physical examination, chest x-ray film, pelvic and hepatic arteriograms, sonogram of the liver and pelvis, complete blood count, and liver and renal function tests, as well as the Australian hepatitis B antigen and antibody test. Prior to July, 1973, only the 24-hour urinary hCG level was serially assayed. After July, 1973, serial serum hCG β-subunit titers were monitored in addition to 24-hour urinary hCG levels. A lumbar puncture was routinely performed and the cerebrospinal fluid was examined for chemistry studies, cytologic tests, and cultures as well as hCG β-subunit titer. When there was clinical suspicion of cerebral metastasis, an elevated cerebrospinal fluid hCG β-subunit titer, or the presence of pulmonary metastasis in which cerebral metastasis was deemed more likely to occur, radionucleotide scan or computed axial tomography of the brain was performed. A repeat curettage was not routinely performed prior to the institution of chemotherapy.

Treatment protocol. Prior to July, 1976, only methotrexate was used in treating the low-risk patients with persistent or metastatic trophoblastic disease at a dosage of 0.4 mg/kg daily intramuscularly for 5 days with a minimum rest period of 7 days. Since July, 1976 methotrexate and citrovorum factor was substituted for methotrexate as follows: Methotrexate was administered intramuscularly at a dosage of 1 mg/kg on days 1, 3, 5, and 7 with folinic acid, 0.1 mg/kg, given intramuscularly on days 2, 4, 6, and 8 starting 30 hours after initial methotrexate administration.

Before July, 1976, patients who developed hepatic toxicity or who attained only a partial response to methotrexate were given actinomycin D at a dosage of 11 to 13 μg/kg intravenously for 5 days, with a similar rest period of 1 week. After July, 1976, patients who developed hepatic toxicity to methotrexate and citrovorum factor were given actinomycin D treatment, but patients who showed resistance or a partial response to the methotrexate and citrovorum factor regimen were subsequently treated with the modified Bagshawe mul-

Table III. Hepatic toxicity evidence by mean peak serum glutamic oxaloacetic transaminase levels

Treatment	*Pretreatment level (μmol/min · L)*	*Posttreatment level (μmol/min · L)*	*Difference**
Methotrexate only	13.92	20.9	6.98
Methotrexate–folinic acid	15.92	49.64	33.72

Normal range: 13 to 30 μmol/min · L.
*$p < 0.025$.

tiagent regimen consisting of hydroxyurea, vincristine, methotrexate, folinic acid, actinomycin D, Cytoxan, and Adriamycin.[4]

All patients were monitored twice weekly by a 24-hour urinary total hCG and, since July, 1973, by twice-weekly serum hCG β-subunit as well. Biochemical remission of gestational trophoblastic disease was defined as the attainment of an hCG β-subunit titer of <5 mIU/ml and/or the attainment of a 24-hour hCG titer of <50 IU for three consecutive weeks. A partial response was defined as more than a 20% fall in a 24-hour urinary hCG or serum hCG β-subunit level following a single course of therapy but failure to induce a subsequent biochemical remission.

Toxicity of chemotherapy was monitored by daily complete blood count and liver and renal function tests during chemotherapy and twice weekly during the rest period. Hepatic toxicity was defined as a threefold increase in the serum glutamic oxaloacetic transaminase level (normal value 13 to 30 μmol/min · L).

Results

Methotrexate alone. Thirty-three patients received only methotrexate treatment with 25 (75.8%) patients achieving sustained complete response. Six patients (18.1%) developed resistance or partial response and biochemical remission was achieved when the chemotherapy was switched to actinomycin D. Two patients (6.1%) had relapse following treatment with methotrexate. One patient responded to multiagent chemotherapy and the other patient died of progressive disease while on a regimen of multiagent chemotherapy. The follow-up of these patients ranged from 8 to 11 years.

None of the patients in this group developed hepatic toxicity. Four had mild leukopenia with the nadir of the leukocyte count between 2000 and 3000/mm^3. The leukopenia was transient and did not delay chemotherapy treatment. Three patients developed mild to moderate thrombocytopenia with platelet counts ranging from 50,000 to 100,000/mm^3. Three patients developed stomatitis. In one, the ulceration was severe enough to require suspension of chemotherapy for 2 weeks.

Methotrexate and citrovorum factor regimen. Sixty-eight patients received methotrexate and citrovorum factor treatment. Fifty-two patients achieved sustained complete biochemical remission. Eight patients (11.8%) had partial response to the methotrexate and citrovorum factor regimen. Permanent biochemical remission was later attained with the modified Bagshawe[4] CHAMOMA regimen. Six patients had the treatment switched to actinomycin D because of hepatic toxicity. All of them have been in biochemical remission since then. Excluding the patients who required change of chemotherapy to actinomycin D because of hepatic toxicity, the corrected sustained remission rate was 83.9% (52 of 62). Two patients developed relapse of disease within a year after methotrexate and citrovorum factor therapy (two of 54, 3.7%). One was resistant to CHAMOMA but responded to high-dose methotrexate combined with intravenous VP16-213 treatment. She has been in remission since then (30 months). One developed resistance to multiagent chemotherapy and died of progressive disease. The follow-up period of these patients ranged from 4 to 9 years.

Table IV. Cumulative induction rate of the responders

Month	*Methotrexate–folinic acid*		*Methotrexate*	
	No.	*%*	*No.*	*%*
First	28/54	51.8	11/27	40.8
Second	49/54	90.7	17/27	62.9
Third	54/54	100	23/27	85

Four patients developed mild leukopenia. One had herpes zoster during chemotherapy. None of them developed thrombocytopenia or stomatitis. Seven patients developed hepatic toxicity; six of them were treated with actinomycin D which resulted in permanent biochemical remission. One did not require any further chemotherapy since she developed hepatic toxicity only during the fourth and the last course of chemotherapy.

Comment

Berkowitz et al.[3] and Smith et al.[5] reported reduced toxicity in patients with gestational trophoblastic disease receiving a methotrexate and citrovorum factor regimen compared with methotrexate alone. In our series, four patients (6%) in the methotrexate and citrovorum factor group developed mild leukopenia, in contrast to

12% of the methotrexate group who had mild leukopenia. The mild leukopenia created no problem. It was transient, causing no delay of chemotherapy. The apparent reduced incidence of leukopenia with methotrexate and citrovorum factor compared with methotrexate alone is not statistically significant. However, thrombocytopenia was significantly higher in the methotrexate group ($p < 0.025$).

Patients treated with methotrexate and citrovorum factor are reported to have a much reduced incidence of hepatotoxicity compared with those treated with methotrexate.[4, 5] Our data showed hepatotoxicity to be significantly higher in the methotrexate and citrovorum factor group ($p < 0.025$). Table III summarizes the hepatic toxicity in the two groups as evidenced by the peak serum glutamic oxaloacetic transaminase level. Hepatitis is endemic in Hong Kong. About 7.4% of the population are hepatitis B antigen positive. This could enhance the hepatotoxicity. Among the seven patients who developed hepatic dysfunction, two were hepatitis B antigen positive. Interestingly, none of them had deranged liver function before chemotherapy and the liver dysfunction reverted to normal after methotrexate and citrovorum factor therapy was stopped. Folinic acid did not appear to prevent hepatic toxicity of methotrexate in these patients. The higher incidence of hepatic toxicity observed in methotrexate and citrovorum factor patients may be due to a much higher dose of methotrexate that we administered and probably also the delayed postmethotrexate rescue with folinic acid (30 hours). In our patients treated with the CHAMOMA regimen, hepatic toxicity was a rare occurrence. The reason may be the earlier folinic acid rescue (12 hours) that we gave. We therefore recommend that folinic acid rescue be given earlier after methotrexate, that is, 24 hours. This is warranted when a higher dose of methotrexate is to be given in regions where hepatitis is endemic.

Berkowitz et al.[3] reported a lower methotrexate resistance rate in the patients receiving methotrexate and citrovorum factor. Smith et al.[5] however, reported a significantly higher methotrexate-resistant tumor incidence in the methotrexate and citrovorum factor group. Our study failed to show any difference in methotrexate resistance between the two groups. The relapse rates of the responders in the methotrexate alone and the methotrexate and citrovorum factor groups were 7.4% (two of 27) and 3.7% (two of 54), respectively ($p > 0.05$). The time required to induce complete biochemical remission in the responders was shorter in the patients treated with the methotrexate–folinic acid regimen ($p < 0.05$). The cumulative induction rate is summarized in Table IV. A shorter induction interval is important in the therapy of gestational trophoblastic disease since most of these patients are asymptomatic. This may reduce the default rate. Once the patient has attained biochemical remission, the default rate would decrease significantly.

Though folinic acid fails to decrease hepatic toxicity of methotrexate in our community, methotrexate–folinic acid therapy is still preferred to methotrexate alone because of its shorter induction interval. The close monitoring of hepatic function in these patients and a prompt change of chemotherapy are ways to prevent subsequent permanent hepatic damage.

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The amniotic band syndrome: Antenatal sonographic diagnosis and potential pitfalls

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Amniotic band syndrome causes a variety of fetal malformations involving the limbs, craniofacial region, and trunk. Six prenatally diagnosed cases of amniotic band syndrome are discussed. The diagnosis was based on sonographic visualization of either amniotic sheets or bands associated with fetal deformation or deformities in nonembryologic distributions known to characterize the amniotic band syndrome. Seven additional cases are considered in which an aberrant sheet of tissue with a free edge was visualized within the amniotic cavity but no restriction of fetal motion or subsequent deformity was demonstrated. (Am J Obstet Gynecol 1985;152:63-8.)

Key words: Amniotic band syndrome, sonography, fetal malformations

The amniotic band syndrome is a common, nonrecurrent cause of various fetal malformations involving the limbs, craniofacial region, and trunk.[1] Recent reports indicate that the incidence of the amniotic band syndrome approximates one per 1200 live births and that many neonates with the amniotic band syndrome have been diagnosed incorrectly as having other forms of congenital malformations.[1,2] Documentation of characteristic features, including clefts and malformations in nonembryologic distributions, asymmetric encephaloceles, and gastropleural schisis, can be suggestive of the amniotic band syndrome even when the bands that caused these deformities are not apparent. Although sonography permits antenatal visualization of typical features of the amniotic band syndrome, to our knowledge in only one case of amniotic band syndrome has the sonographic diagnosis been made before birth.[3] In one additional case the sonographic documentation of "discordant" anencephaly in a twin pregnancy alerted the obstetrician to the presence of congenital deformity, but the antenatal diagnosis of the amniotic band syndrome was not rendered.[4]

Advances in sonographic resolution capabilities now permit frequent visualization of membranes or membrane-like structures within the uterus (Fig. 1). For example, segments of amniotic membrane that have not yet fused with the chorion can be visualized normally in the first 16 weeks of gestation.[5] Also, subamniotic and subchorionic fluid collections occurring at anytime during pregnancy may render these membranes visible. However, we have also observed aberrant sheets of tissue with a free edge that clearly project into the lumen of the amniotic cavity and may mimic "amniotic bands" but that do not result in the amniotic band syndrome (Fig. 2).

Because the amniotic band syndrome is a sporadic disorder that may mimic recurrent disorders, appropriate genetic counseling requires accurate diagnosis. Conversely, when sonography visualizes an aberrant sheet of tissue with a free edge within the amniotic fluid, accurate assessment of normal fetal morphology avoids the false positive diagnosis of the amniotic band syndrome that might lead to termination of a potentially normal pregnancy.

We herein report five additional cases of the amniotic band syndrome diagnosed before birth on the basis of sonographic visualization of either amniotic sheets or bands with associated fetal deformities or deformities in nonembryologic distributions characteristic of the amniotic band syndrome. We also report seven infants without the amniotic band syndrome in whom antenatal sonography visualized an aberrant sheet of tissue with a free edge in the amniotic fluid but normal fetal morphologic features.

Case material

Table I summarizes the sonographic and follow-up data regarding the six cases in which the antenatal sonographic diagnosis of the amniotic band syndrome was made. Case 2 has been reported previously from this institution.[3] In two cases, an amniotic sheet or bands were seen attached to fetal parts and were associated with fetal edema, deformity, and/or restriction of motion (Fig. 3). In the other four cases, no aberrant sheets

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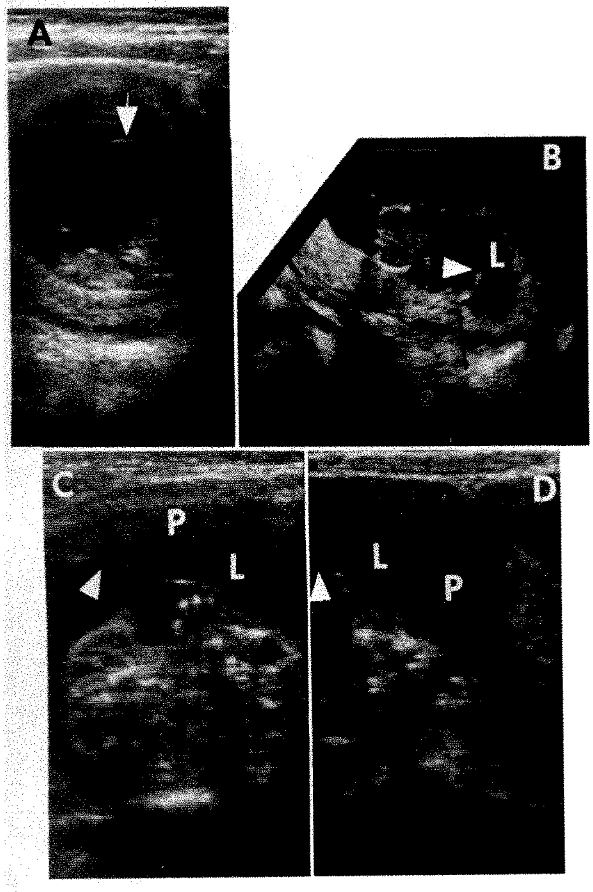

Fig. 1. Examples of intrauterine membranes or membrane-like structures that do not have a free edge within the amniotic fluid. The absence of a free edge distinguishes these structures from the aberrant sheets of tissue that may mimic amniotic bands. *A*, Portions of the amnion *(arrow)* that have not yet fused with the chorion are visible in this fetus at 11 menstrual weeks. *B*, A subchorionic lucency *(L)* compatible with extrachorionic hemorrhage extends to the edge of the placenta *(P)* *(black arrow)*. The extrachorionic hemorrhage creates a membrane-like structure *(white arrow)* in this first-trimester pregnancy complicated by vaginal bleeding. *C*, and *D*, Lucency between the placenta *(P)* and the amnion *(arrow head)* produces a membrane-like structure without a free edge. This represents amniochorionic separation.

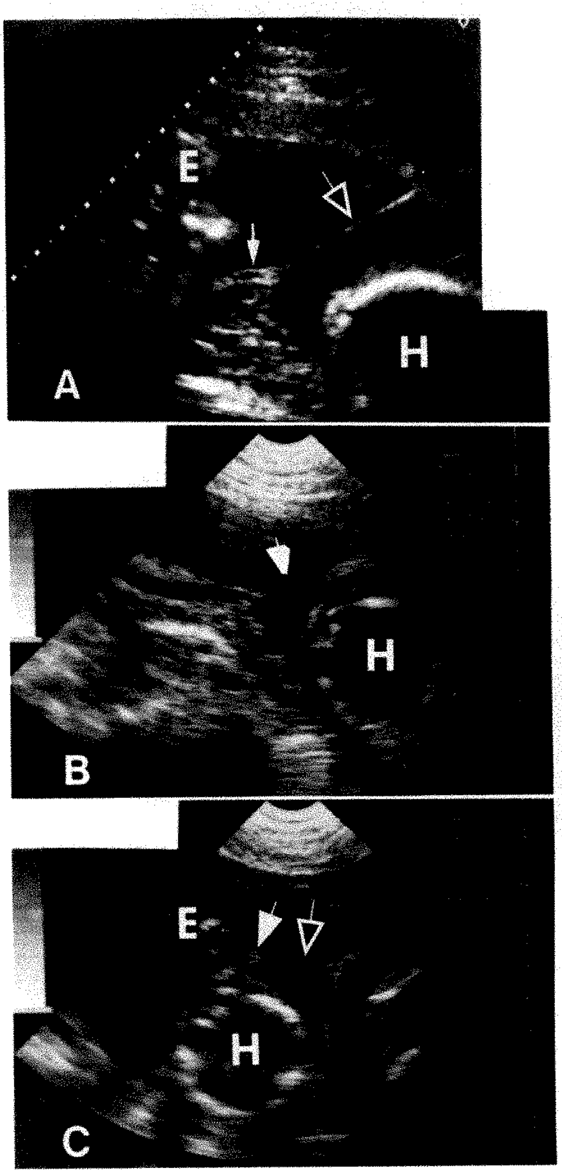

Fig. 2. Real-time scans display an aberrant sheet of tissue with a free edge within the amniotic fluid (Case 9). This pregnancy resulted in a normal infant. *A*, Although fetal parts (*H* = head, *E* = extremity) bridge the sheet of tissue *(open arrow)*, there was no fetal deformity, edema, or restriction of motion. Note the broad base of the aberrant sheet of tissue *(small closed arrow)*. *B*, This scan plane sections longitudinally through the thickened free edge of the sheet of tissue *(closed arrow)* (*H* = head). *C*, In this plane of section, which images the aberrant sheet of tissue transversely, the sheet of tissue appears bandlike *(open arrow)*. Again noted is its bulbous free edge *(closed arrow)* as well as the bridging fetal parts (*H* = head, *E* = extremity).

or bands of tissue were seen in the amniotic fluid, possibly because of concomitant oligohydramnios, but characteristic deformities in nonembryologic distributions permitted the antenatal diagnosis of the amniotic band syndrome. Follow-up pathologic evaluation confirmed the presence of the amniotic band syndrome in each case.

Table II provides analogous data regarding the seven cases in which we observed an aberrant sheet of tissue with a free edge in the amniotic fluid but no associated fetal deformity or entrapment (Fig. 2). Sheets of aberrant tissue were distinguished from other causes of intrauterine membranes by their free edge within the amniotic fluid.[5] In each case only a single sheet of aberrant tissue was visible. In two instances a sheet of tissue that had been seen earlier in pregnancy was no longer visible later in pregnancy. Although the sheet of tissue touched five of the fetuses, in none did it appear attached to the fetus; the fetus was able to alter its position relative to the sheet of tissue. Similarly, although fetal

Table I. Sonographic and follow-up data regarding the six cases in which diagnosis of amniotic band syndrome was made on basis of antenatal sonogram (case 2 has been reported previously[3])

Case No.	*Reason for sonography*	*Menstrual age (wk)*	*Sheet or bands*	*Single or multiple*	*Attached to or touching fetus*	*Bridging fetal parts*	*Associated edema, deformity*	*Restriction of motion*	*Other deformities*	*Follow-up*
Amniotic sheet or bands associated with fetal deformity										
1	Twins; anomaly on outside sonogram (?)	21	Bands	Multiple	Attached	Numerous	Multiple facial clefts	Yes	Asymmetric encephalocele	Amniotic band syndrome (autopsy)
2	Maternal drug abuse	21	Sheet	Single	Attached	Numerous	Asymmetric edema	Yes	No	Amniotic band syndrome (autopsy)
Fetal deformities in nonembryonic distributions; aberrant sheets or bands not visualized										
3	Omphalocele on outside sonogram	37	—	—	—	—	One leg absent	—	Gastroschisis with exteriorization of liver and bowel	Amniotic band syndrome (autopsy)
4	Abnormalities on outside sonogram	25	—	—	—	—	One leg absent	—	Gastropleural schisis with exteriorization of liver, bowel, and heart	Amniotic band syndrome (autopsy)
5	Anomalies on outside sonogram (?)	22	—	—	—	—	—	—	Gastropleural schisis with exteriorization of liver and heart, asymmetric encephalocele	Amniotic band syndrome (autopsy)
6	Omphalocele on outside sonogram (?)	30	—	—	—	—	—	—	Gastroschisis with exteriorization of liver and bowel, marked scoliosis, small thorax	Amniotic band syndrome (autopsy)

parts intermittently bridged the aberrant sheet of tissue in three instances, in no case was there associated fetal deformity or restriction of motion. Each pregnancy resulted in an infant without evidence of the amniotic band syndrome. In Case 12, sonography also demonstrated evidence of alobar holoprosencephaly, a developmental anomaly not related to the amniotic band syndrome.

Comment

Most contemporary authors concur with the hypothesis elaborated by Torpin[6] in 1968, which explains the characteristic clinical features of the amniotic band syndrome.[1, 3-5, 7-10] Torpin asserted that rupture of the amnion leads to subsequent entanglement of various embryonic or fetal parts by fibrous mesodermic bands that emanate from the chorionic side of the amnion. Entrapment of fetal parts by the bands may cause lymphedema, amputation, or slash defects in nonembryologic distributions. Torpin further suggested that the amnion, which is contiguous with the fetal skin at the umbilicus, protects the fetus from contact with the chorion. When disruption of the amnion occurs, the fetus may adhere to and fuse with the chorion with subsequent maldevelopment of the subjacent fetal tissue.

Although the amniotic band syndrome manifests variable patterns of deformity, a proclivity for certain anomalies typifies the disorder and permits prenatal diagnosis. For example, exteriorization of the liver rarely occurs with gastroschisis.[11, 12] However, in each of our four fetuses who had gastroschisis associated with the amniotic band syndrome, hepatic exteriorization occurred. This suggests that when gastroschisis results in exteriorization of the liver the amniotic band syndrome should be strongly considered.

Similarly, approximately 90% of encephaloceles occur in the midline because of failure of neural tube fusion.[13] In both of our fetuses with an encephalocele associated with the amniotic band syndrome the encephalocele occurred laterally. Therefore, identification of an asymmetric encephalocele should strongly suggest the amniotic band syndrome, although asymmetric encephaloceles can occur without amniotic band syndrome. Other craniofacial malformations such as asymmetric anencephaly and bizarre clefting patterns should also suggest the amniotic band syndrome. Cleft

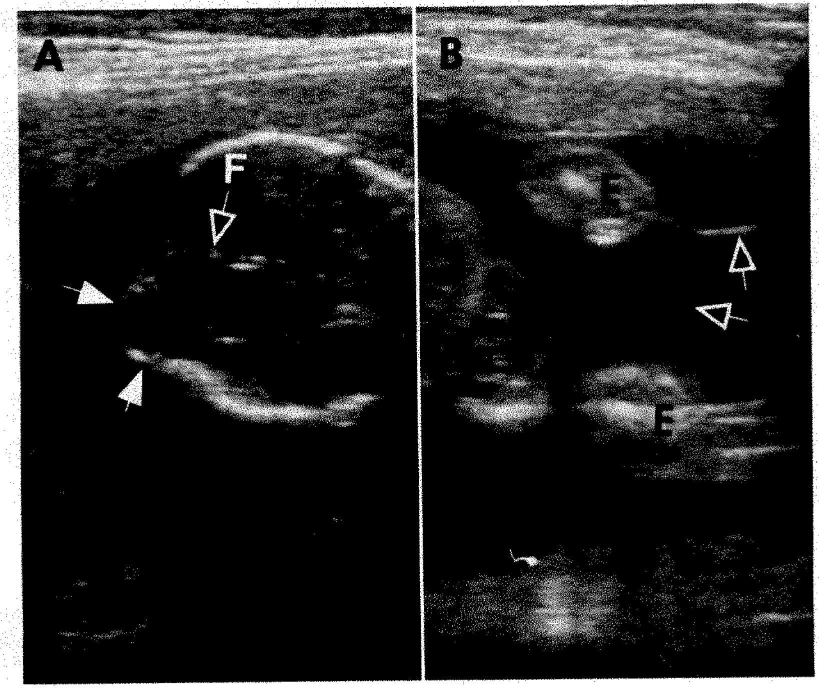

Fig. 3. Representative sonograms of a fetus (Case 1) with the amniotic band syndrome. A, Scan through the fetal head demonstrates an asymmetrical encephalocele *(solid arrows)* (*F* = falx cerebri). B, Numerous bands *(arrows)* are attached to the fetal extremities *(E)* and restrict fetal motion. Other scans showed facial clefts in a nonembryologic distribution. These features enabled an antenatal diagnosis of the amniotic band syndrome.

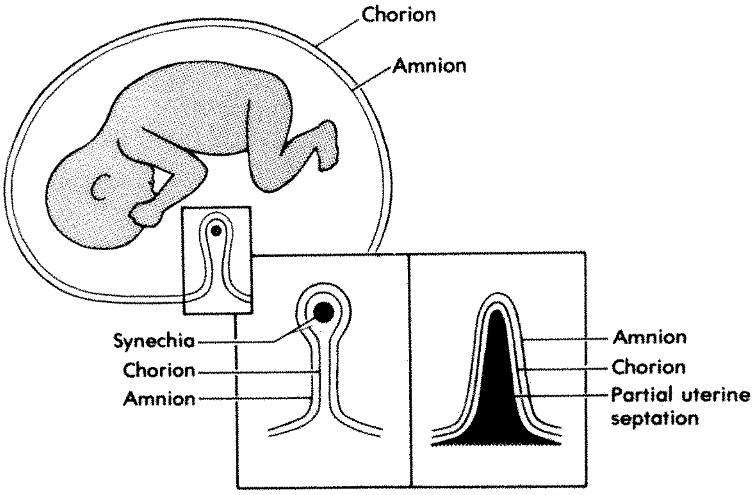

Fig. 4. Schematic drawing of the gravid uterus. Amnion and chorion extend over a uterine synechia or partial septation. This creates a sheet of aberrant tissue with a free edge within the amniotic fluid. Despite the "free" edge, the amnion is not disrupted. Although fetal parts may bridge or touch the aberrant sheet of tissue, there is no associated fetal deformity or restriction of motion. This appearance is not associated with the amniotic band syndrome.

lip and palate are common paramedian or median malformations that occur in characteristic patterns caused by failure of fusion of the paraxial mesodermic masses.[14] Although they may occur in association with other congenital anomalies, there is no reported increased incidence with asymmetric encephaloceles, gastropleural schisis, or multiple amputations. On the other hand, facial fissures associated with the amniotic band syndrome form in bizarre, nonembryologic patterns.

Table II. Sonographic and follow-up data regarding the seven cases in which an aberrant sheet of tissue with a free edge in the amniotic fluid was present but there were no associated fetal deformities

Case No.	*Reason for sonogram*	*Menstrual age (wk)*	*Sheet or bands*	*Single or multiple*	*Attached to or touching fetus*	*Bridging fetal parts*	*Associated edema, deformity*	*Restriction of motion*	*Other deformities*	*Follow-up*
7	Size-dates discrepancy	13	Sheet	Single	Touching fetus	None	None	None	None	Normal infant
		21	Not visible	—	—	—	None	None	None	
8	Previous holoprosencephaly	19	Sheet	Single	Extremity, trunk	Head	None	None	None	Normal infant
		25, 29, 38	Sheet	Single	Neither	None	None	None	None	
9	Maternal age (35 yr)	17	Sheet	Single	Neither	None	None	None	None	Normal infant
		20	Sheet	Single	Touching neck	Leg	None	None	None	
		23-33 (every 2-5 wk)	Sheet	Single	Neither	None	None	None	None	
10	Previous fetal death	34	Sheet	Single	Neither	None	None	None	None	Normal infant
11	Size-dates discrepancy	17	Sheet	Single	Neither	Umbilical cord	None	None	None	Normal infant
		23	Sheet	Single	Touching legs, trunk	None	None	None	None	Normal infant
		25, 29	Sheet	Single	Neither	None	None	None	None	
		32	Not visible	—	—	—	None	None	None	
12	Maternal diabetes	29	Sheet	Single	Touching occiput	None	None	None	Alobar holoprosencephaly	Stillborn at 30 menstrual weeks with alobar holoprosencephaly, otherwise normal
13	Amniotic band on outside sonogram (?)	20	Sheet	Single	Neither	None	None	None	None	Normal

Although extremity amputations may result from genetic or teratogenic causes, several distinguishing features permit identification of amputations related to the amniotic band syndrome.[6] Whereas genetic or teratogenic amputations tend to be bilaterally symmetrical, amputations caused by the amniotic band syndrome are usually asymmetric. While syndactyly that involves the base of the digits implies genetic or teratogenic causes, syndactylism that originates distally suggests the amniotic band syndrome. Identification of a fibrous band of tissue within a constricting ring with distal elephantiasis or protrusion of uncovered bone distal to the soft tissue at the site of amputation constitute pathognomonic signs of the amniotic band syndrome. Such fibrous bands also can be found when facial fissures are caused by this syndrome. Constriction of the umbilical cord by an amniotic band represents potential "amputation" at its most extreme. Among 36 fetuses with umbilical cord constriction identified by Torpin,[6] none survived.

When antenatal sonography visualizes an aberrant sheet or bands of tissue attached to a fetus with characteristic deformities and restriction of motion, a diagnosis of the amniotic band syndrome can be made. Even when the aberrant sheets or bands are not visualized, characteristic fetal deformities in nonembryologic distributions provide evidence highly suggestive of the amniotic band syndrome. Such information will alert the perinatalogist and geneticist to obtain a detailed postnatal examination. On confirmation of the diagnosis, appropriate counseling can be performed. The recurrence risk for the aberrant bands and any consequences thereof appear to be negligible.[10]

Aberrant sheets of tissue with a free edge within the amniotic fluid often occur in the absence of the amniotic band syndrome. During Torpin's[6] extensive review of 400 fetuses with amnion rupture, he discovered only three cases in which the fetus escaped injury. In contrast, all seven of the pregnancies in the current study in which we visualized a single aberrant sheet of tissue within the amniotic fluid but no associated fetal deformity resulted in infants without the amniotic band syndrome. The sonographically visible aberrant tissue within the amniotic fluid in these cases may represent intact amnion and chorion extending over a partial uterine septation or synechia (Fig. 4). That the base or free edge of the aberrant sheet of tissue often appeared disproportionately thickened supports this hypothesis. Furthermore, we are aware of an additional case with similar findings in a woman with uterine synechia documented by hysterosalpingography (Rich P, personal communication). Finally, in two instances the aberrant sheet disappeared as the uterus enlarged. Possible explanations of this sequence are that a synechia was stretched beyond its tensile strength, permitting rupture and disappearance of the observed abnormality, or that the sheet was simply compressed against the uterus by growth of the fetus and thus became imperceptible.

In the above-described seven cases there would be no chance for fetal entanglement and only a very small chance for entrapment of fetal parts. Therefore antenatal sonographic demonstration of a sheet of aberrant tissue in the amniotic fluid surrounding a fetus without evidence of associated deformity does not imply the presence of the amniotic band syndrome. This finding alone does not constitute sufficient indication for elective pregnancy termination.

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Surface changes in intrauterine contraceptive devices after variable use

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Four used intrauterine contraceptive devices and two new control devices were studied by scanning electron microscopy. All intrauterine contraceptive devices were found to have surface deposits that differed not only from site to site on a given device but between devices. A finding of this study not previously described in the literature was the observation of a euhedral crystal rosette of an apatite mineral group [$Ca_5(PO_4)_3(F,Cl,OH)$] on the Lippes Loop that had been in situ for 15 years. (AM J OBSTET GYNECOL 1985;152:69-78.)

Key words: IUDs, scanning electron microscopy, apatite minerals

Intrauterine contraceptive devices (IUDs) have had widespread clinical application for more than two decades. Although a vast literature regarding the long-term safety and efficacy of IUDs has developed, relatively few reports have been published regarding morphologic changes on their surfaces after long-term use. Numerous questions remain unanswered regarding these surface deposits. They include: (1) How diverse is the variation in the composition and crystallography of the various binding anionic complexes on the surface of the IUD or its string? (2) Are the surface changes observed on the IUD itself and the intrauterine and vaginal portions of the string similar or dissimilar? (3) What is the underlying physiologic mechanism of these changes?

Our interest in this subject began when a patient without symptoms requested removal of a Lippes Loop after 15 years of use. Because one of the vaginal strings appeared black and "moldy," scanning electron microscopy of the IUD and its string was performed. Subsequently additional IUDs of varying types (Saf-T-Coil, Cu-7, and Cu-T) were analyzed. When energy dispersive analysis of the Lippes Loop demonstrated the presence of an apatite mineral group [$Ca_5(PO_4)_3(F,Cl,OH)$] similar to that described in dental plaque, human teeth and denture material were also studied for comparison.

Table I. Types of IUDs and clinical status

IUD No.	*IUD type*	*Length in situ*
1	Lippes Loop No. 1	15 Yr
2	Cu-7 No. 1	Control
3	Lippes Loop No. 2	Control
4	Saf-T-Coil No. 1	8 Yr
5	Cu-7 No. 2	4 Yr
6	Cu-T No. 1	6½ Yr

Material and methods

Table I describes types of IUDs and duration of their use. For comparison, a new Cu-7 and Lippes Loop were also studied. IUDs numbered 1, 4, 5, and 6 were placed in 2.5% glutaraldehyde in Millonig's buffer (pH 7.3) immediately after their removal. Unused ("control") IUDs (Nos. 2 and 3) were also placed in glutaraldehyde immediately after removal from their sterile envelopes. After suitable fixation, all specimens were prepared for scanning electron microscopy according to standard techniques. Samples were mounted on aluminum studs and vacuum evaporated with gold-palladium in a ratio of 60:40. A JEOL JSM 50A scanning electron microscope was used; photographs were taken with Polaroid P/N 55 film.

Results

Lippes Loop. The intrauterine portion of one of the two strings of this IUD (IUD No. 1, Table I) demonstrated an irregular distribution of plaquelike encrustation with a smooth string surface visible underneath the plaque (Fig. 1). In contrast, part of the intravaginal portion of the second string was so heavily encrusted that the underlying surface was not visible at any point (Fig. 2).

The body of the Lippes Loop showed two different encrustation morphologic characteristics. These were

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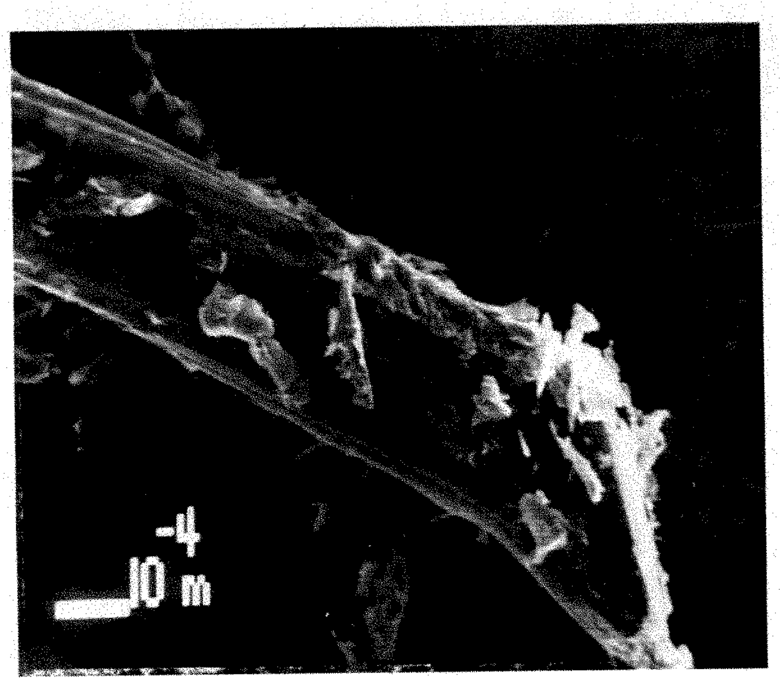

Fig. 1. Lippes Loop No. 1. Plaquelike encrustation on surface of intrauterine portion of nylon string. (Original magnification ×100.)

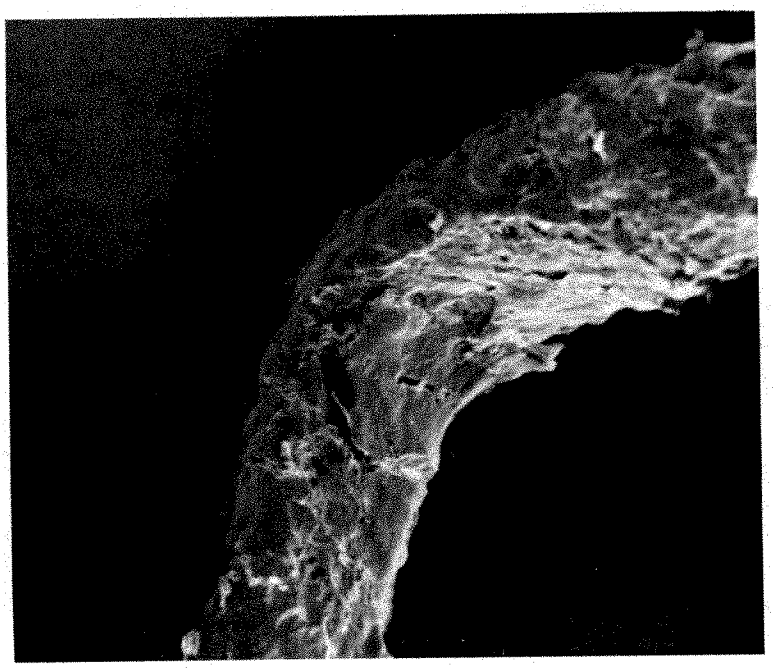

Fig. 2. Lippes Loop No. 1. Vaginal portion of nylon string completely encrusted. (Original magnification ×80.)

seen on both sides of the clearly visible molding mark that bisects the IUD (Fig. 3). One pattern had the appearance of a continuous mud-cracked encrustation. On low-power (40×) magnification this surface morphology looked like a dried riverbed or other natural geographic formation in which crevasses mar the surface integrity. On higher (3000×) magnification this surface appeared stippled (Fig. 4). On a more superior portion of the IUD body (Fig. 3), several rounded masses appeared to project from the surface. At 800× magnification these masses were found to be rosettes of euhedral crystals with a columnar prismatic habit.

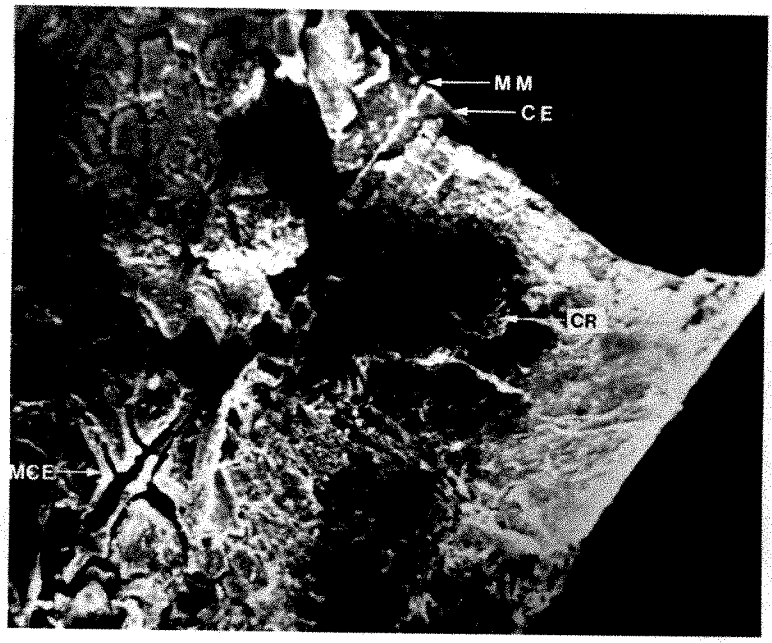

Fig. 3. Lippes Loop No. 1. IUD body with continuous mud-cracked encrustation *(MCE)* to the *left* and superior to molding mark *(MU)*; crystal rosettes *(CR)* seen to the *right* and inferior to molding mark. The cut edge is shown as *CE*. (Original magnification ×40.)

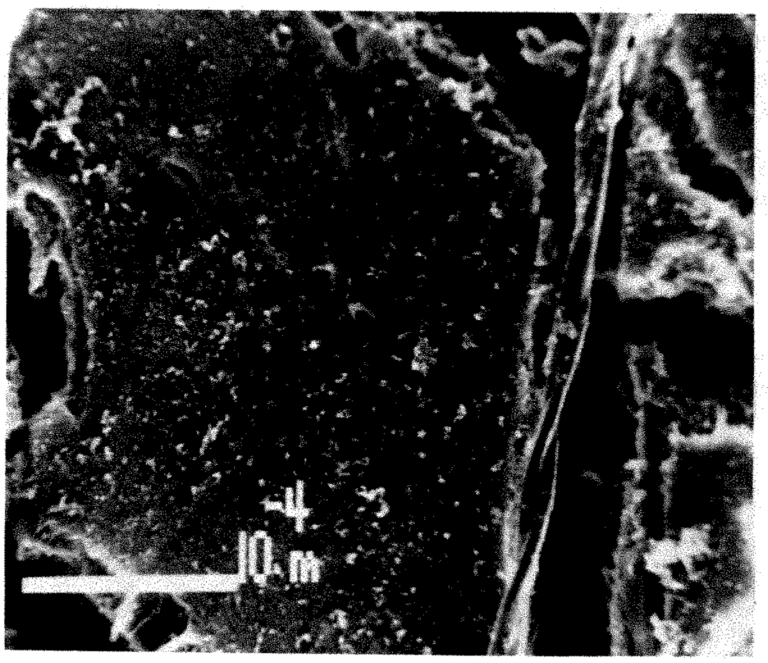

Fig. 4. Lippes Loop No. 1. High-power magnification of plaque in Fig. 3. (Original magnification ×3000.

The porous nature of the end of each separate crystal is clearly visible (Fig. 5).

Saf-T-Coil. Some observations of this IUD (IUD No. 4, Table I) were similar to those of the Lippes Loop; others were dissimilar. The dissimilarity centered around the absence of euhedral crystalline forms and the presence of "bulbous nodules" (Fig. 6) surrounded by plaquelike encrustation that appeared fibrous at times and granular at others. In some areas a netlike matrix was visible (Fig. 7), suggesting that the nodules represented filled-in areas of a fibrous network. On other areas of the IUD the superficial encrustations

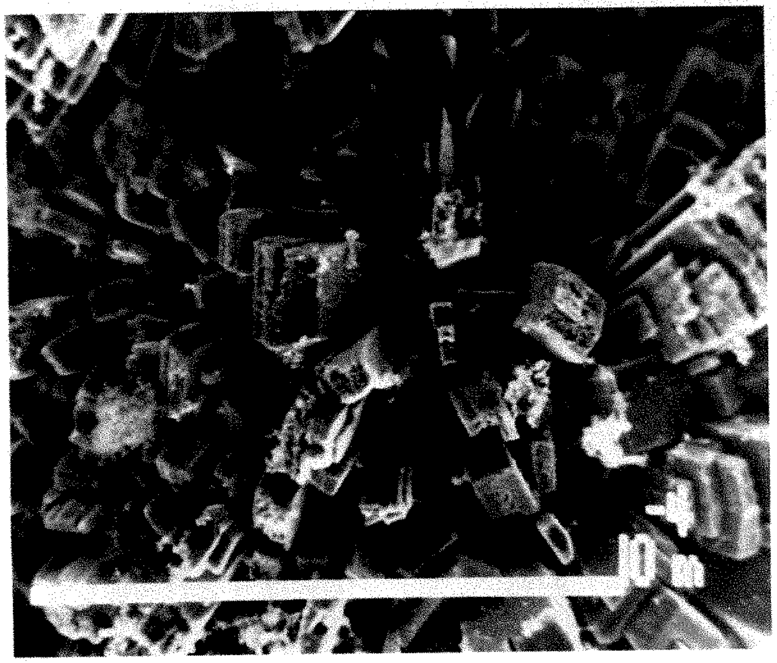

Fig. 5. Lippes Loop No. 1. High-power view of rounded masses in Fig. 3. (Original magnification ×800.)

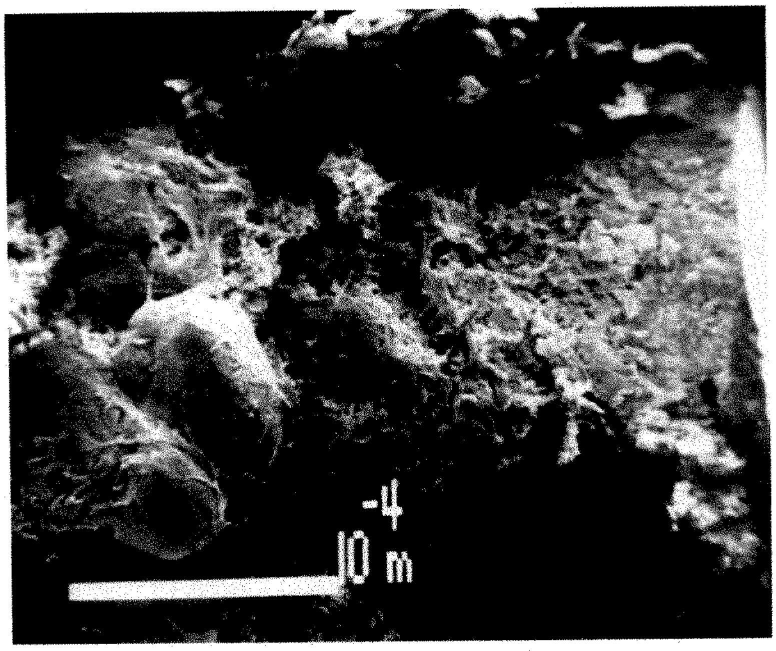

Fig. 6. Saf-T-Coil No. 1. IUD body with "bulbous nodules" surrounded by granular and fibrous-appearing plaque. (Original magnification ×40.)

had broken off revealing an underlying and more regular granular base to plaque on the IUD surface (Fig. 8).

An observation not seen on any other device examined was the presence of spaghetti-like structures projecting from a coherent base of the plaquelike encrustation (Fig. 9) on the intrauterine portion of string of this device. Closer examination of the individual threads suggested that the mechanism of this formation may have been the result of cohesion of a series of droplike particles or may represent organic material.

Cu-7. The observations of this IUD (IUD No. 5,

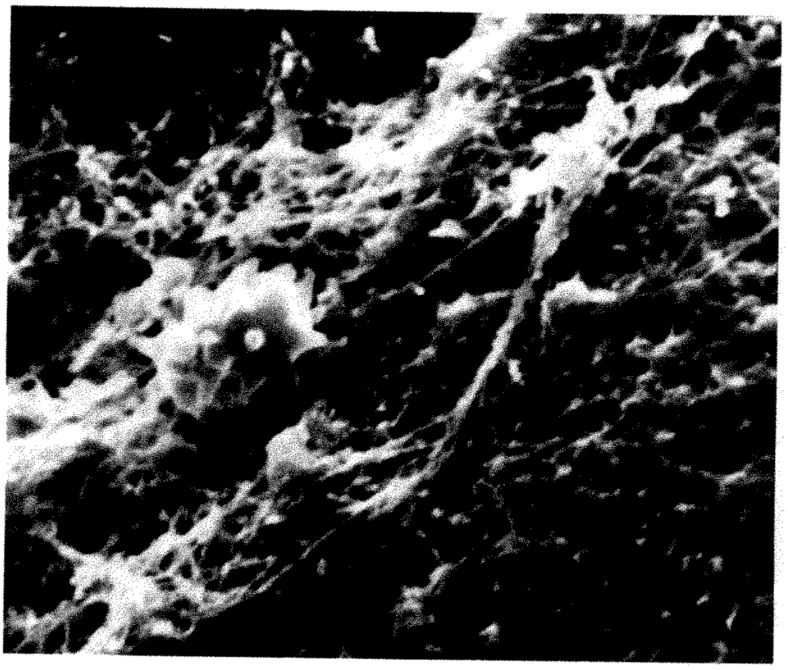

Fig. 7. Saf-T-Coil No. 1. High-power magnification of surface of plaquelike encrustation shows netlike matrix. (Original magnification ×4000.)

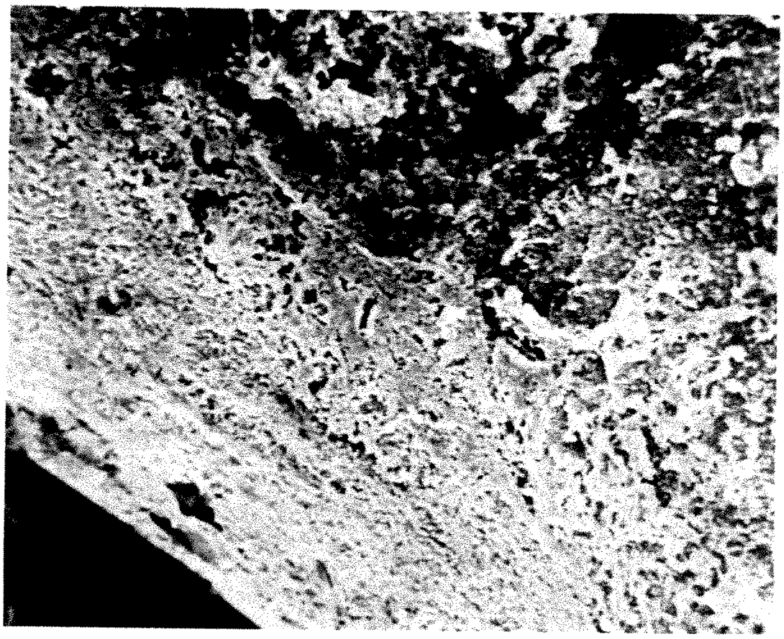

Fig. 8. Saf-T-Coil No. 1. IUD body with base layer of plaquelike encrustation. (Original magnification ×100.)

Table I) were characterized by thick and dense encrustation; "bulbous nodules" were absent (Fig. 10). With higher magnification the fibrous and granular character of these deposits was visible (Fig. 10, *inset*). The surface of the IUD body and its string had plaquelike encrustations with a more textured appearance (Fig. 11 and Fig. 11, *inset*).

Cu-T. There were two notable features to the encrustation of this IUD (IUD No. 6, Table I). The first (Fig. 12) was the thick and contiguous nature of the encrustation. This was especially apparent around the area of the knot and the copper wire. Fragmentation of this encrustation was easily visible. The second (Fig. 13) distinguishing feature was that at higher magnifi-

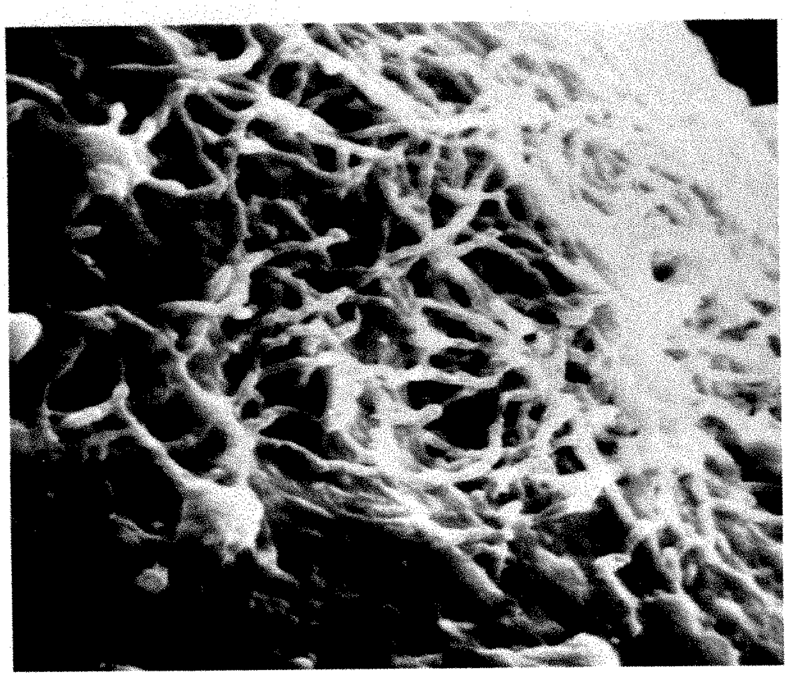

Fig. 9. Saf-T-Coil No. 1. High-power view of intrauterine portion of string with spaghetti-like threads. (Original magnification ×1300.)

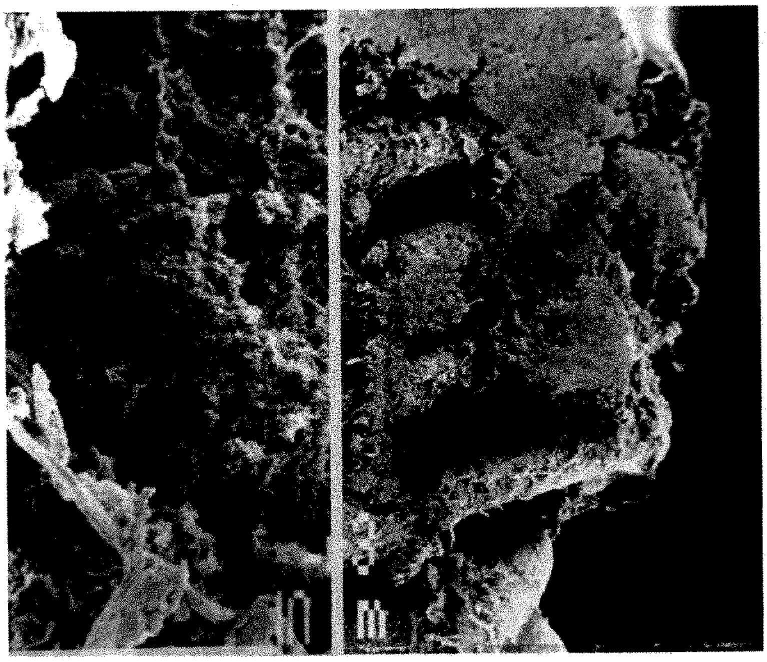

Fig. 10. Cu-7 No. 2. Copper coils partially covered by dense and fibrous plaquelike encrustation. (Original magnification ×30.) *Inset (left)*, high-power view of fibrous and granular nature of deposits. (Original magnification ×500.)

cation the material underlying the fragmentated superficial surface encrustations revealed a series of symmetrical cracks in an underlying base coating.

Controls. The two unused control IUDs (IUD Nos. 2 and 3, Table I) revealed smooth, featureless surface structures at low magnification. As magnification was increased, the inherent surface morphologic features became clearly evident and the impressions of the injection molding process could be seen.

Human teeth. The micrographs of human teeth showed the presence of surface morphologic features similar to those observed on portions of various IUDs and their strings. This was particularly apparent at low (20×) magnification (Fig. 14). At high magnifications

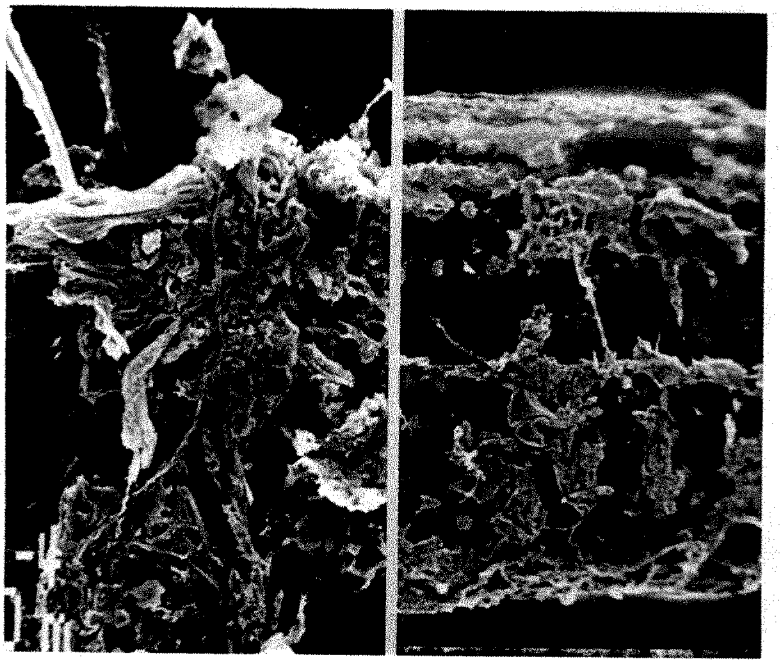

Fig. 11. Cu-7 No. 2. Textured appearance of surface of IUD body. Molding mark visible. (Original magnification ×20.) *Inset (left).* Detail of same. (Original magnification ×100.)

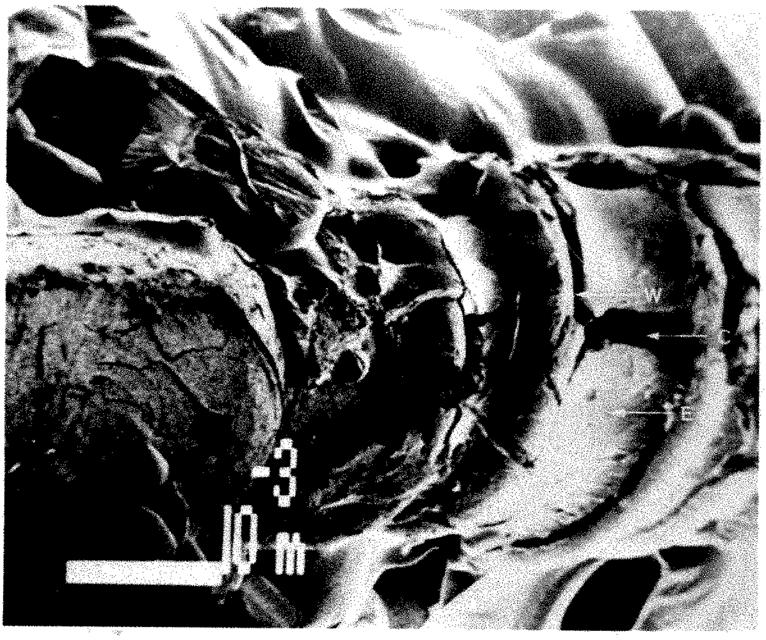

Fig. 12. Cu-T No. 1. Fragmentation and cracking *(C)* of heavy surface encrustation *(E)*. Copper wire is shown as *W*. (Original magnification ×20.)

the delicate coalescence of a fibrous matrix was seen on some views, and on others (viewed tangentially) a very delicate infrastructure of thin, perpendicular, tendril-like structures was seen (Fig. 15).

Comment

Previously published studies of the surfaces of various IUDs used for varying lengths of time have demonstrated the presence of adherent material.[1-10] Depending on the nature and methodology of the study, a variety of substances have been described. Major areas of interest to date have included the analysis of the chemical nature of the surface encrustation[1, 2, 4-7] and the elucidation of the cellular components of the proteinaceous material found on some, but not all, IUDs shortly after their removal.[3, 7, 9, 11]

Wide variations exist in the microenvironments with which an IUD is in contact. These microenvironments

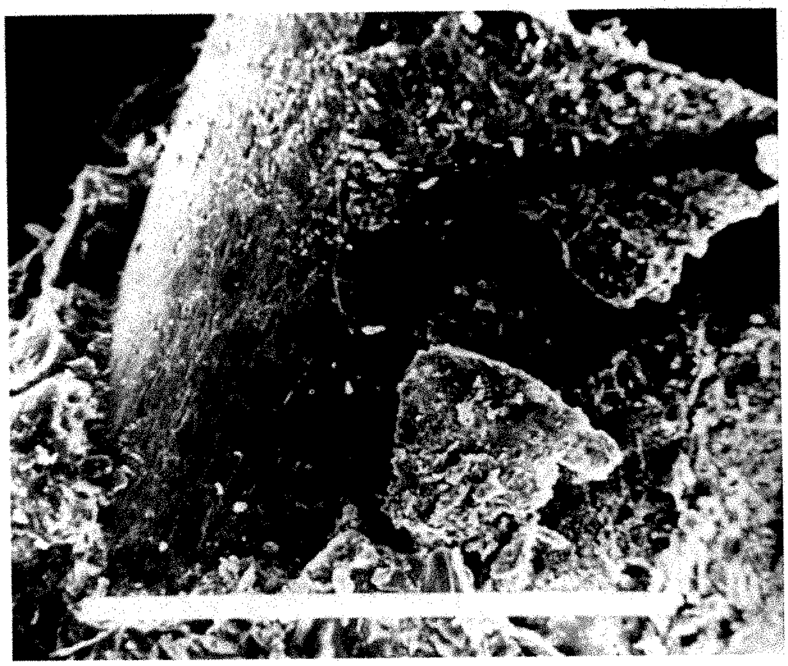

Fig. 13. Cu-T No. 1. Tangential view showing superficial encrustation in fragments, symmetrical cracks in base coating, and side view of thick superficial encrustation *(far left)*. (Original magnification ×80.)

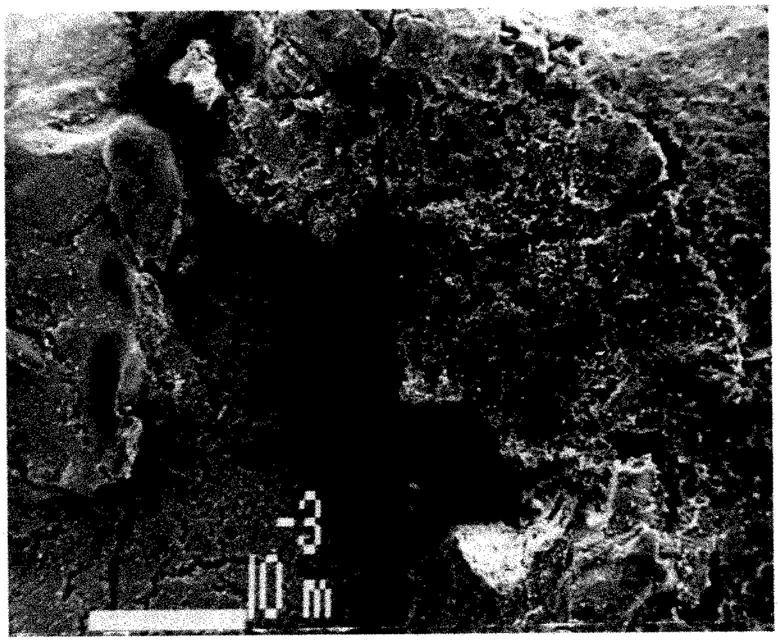

Fig. 14. Human tooth No. 1. Low magnification shows mud-cracked plaquelike encrustation. (Original magnification ×20.)

are separated by short distances, often centimeters apart. The biochemical reactions occurring around the IUD at its leading end differ from those surrounding its trailing end, regardless of whether the IUD has a fundal placement or rests in the lower uterine segment. The same may be said for the tail. The leading end of the tail is in the endometrial cavity while the middle portion lies in the endocervical canal, and the trailing portion hangs within the vaginal epithelial tube. In the case of the trailing portion of the string the microenvironment surrounding the upper portion of the vaginal string is different from that surrounding the most distal portion. These variations in specific microenvironments include not only biochemical differences but also diffferences in the microflora.

A new finding from this study was the observation

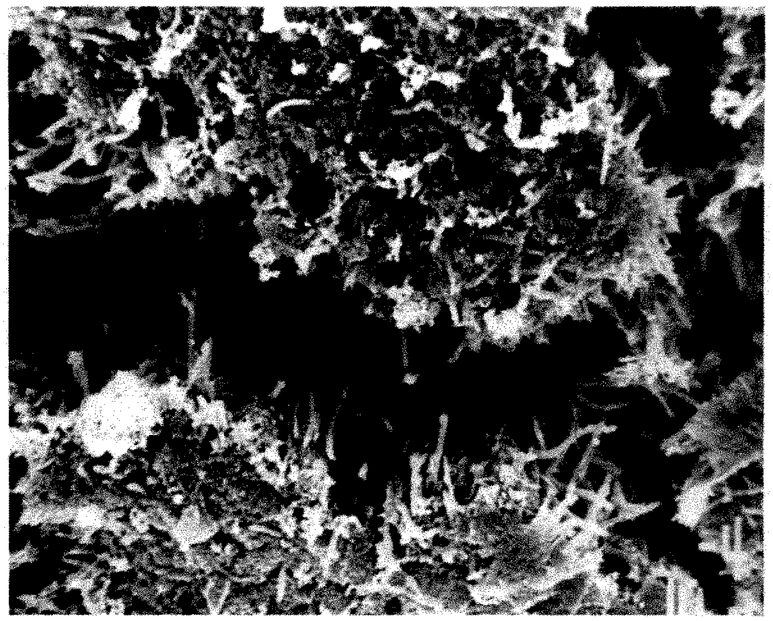

Fig. 15. Human tooth No. 1. High-power magnification shows perpendicular tendril-like structures. (Original magnification ×800.)

of rosettes of euhedral apatite crystals on the body of the 15-year in situ Lippes Loop. Calcium apatite in noncrystalline form is commonly found along with calcium carbonate in calculus on teeth. Schmidt[12] has hypothesized that the mechanism of deposition of calcium is similar on teeth and IUDs. We are unable to explain the significance of the rosette formations other than to state that environmental conditions were correct for perfect crystalline growth. To our knowledge, this phenomenon has not been described previously in the literature.

Bank et al.[7] have observed (and we fully agree) that the process of visual orientation of IUD specimens is difficult when surface deposits are examined at high magnification. The apparently distinct morphologic layers of surface debris may result from stratification of deposited material over time. The appearance of a given section of encrustation varied with the degree of magnification. For example, when an IUD or its string was observed under low-power magnification, the demarcation between the IUD surface and the adherent material was clearly visible. However, when magnification was increased the visual relationship of the adherent material to the IUD surface often was lost. On the other hand, when the mount was held in the same place and the magnification varied, the viewer could appreciate that what was present represented material adherent to the IUD surface. Had a high-power view been chosen (without serial diminutions in magnification for corroboration), the viewer might have come to the erroneous conclusion that the IUD or its string had undergone a process of structural degradation.

At present no uniformity exists in the descriptive terminology used to characterize IUD surface changes. The formations described in this article as "bulbous nodules" (Fig. 6) have been called "hemispherical projections" by Bank et al.[7] Some of the fragmentation observed in this and other studies[1, 7] and described by us as "mud cracking" on the Lippes Loop and the Cu-T may be artifactual and caused by specimen preparation.

Our findings generally agree with those already present in the literature. The consensus is that these surface changes are generic to all IUDs although they vary from site to site on a given IUD, between two IUDs of the same type, and/or between IUDs of different types. The variations noted between different IUDs and between different portions or segments of the same IUD are probably more dependent on individual variations in the biochemical milieu surrounding the IUD than they are on differences between IUD types.

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Plasma dextran levels after abdominal instillation of 32% dextran 70: Evidence for prolonged intraperitoneal retention

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Postoperative ascites in patients receiving intraperitoneal dextran 70 may result from slow absorption. We tested this by instilling 250 ml of dextran 70 into the peritoneal cavity of patients undergoing tuboplasty. Serum dextran levels were undetectable until 24 hours after operation and rose during the next 4 days. Ascites in patients with intraperitoneal dextran 70 results from third spacing in response to the persistent osmotic load. (Am J Obstet Gynecol 1985;152:78-9.)

Kew words: Adhesions, dextran, infertility

Recently we evaluated the formation of adhesions in infertility patients after distal salpingostomy who had received intraoperative instillation of 32% dextran 70 or saline solution. We found, via laparoscopy 6 to 12 weeks later, that although the majority of patients in both treatment groups benefited from the surgical procedures in terms of reduction in pelvic adhesions and improved tubal patency, those who received intraperitoneal dextran 70 therapy had a greater reduction of adhesions in the dependent portion of the pelvis compared with the patients treated with saline solution.[1] Since most of the patients treated with dextran 70 developed a clinically apparent ascites, we hypothesized that the hyperosmolar intraperitoneal dextran 70 solution was equilibrated by movement of extraperitoneal fluid into the abdominal cavity. This implies that dextran is metabolized and slowly absorbed into the blood stream during the postoperative interval.

In this study we tested this hypothesis by instilling 250 ml of dextran 70 into the peritoneal cavity of infertility patients before the completion of tuboplasty. Thereafter serial plasma determinations of dextran concentrations were performed.

Methods

Patients complaining of infertility caused by tubal obstruction signed an informed consent approved by the Human Subjects Committee of St. Vincent's Hospital. These women were healthy, aged 23 to 32 years, and complained of no acute disease. After the completion of a routine salpingostomy, 250 ml of Hyskon (Pharmacia Laboratories, Piscataway, New Jersey) was instilled into the pelvis. Thereafter the peritoneum was closed with a running absorbable suture and the patient was allowed to undergo routine postoperative recovery.

Blood was drawn from an antecubital vein 2 hours before operation, 1 and 3 hours after operation, and 1, 2, 3, and 4 days after operation. Blood was allowed to clot, and serum was collected by centrifugation and frozen (4° C) until assay. Plasma dextran determinations were performed by the method of Roe.[2] The trichloroacetic acid filtrate (Whatman No. 42, Whatman

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Table I. Plasma concentration of dextran 70 (milligrams per milliliter) after intraperitoneal instillation (250 ml) after salpingostomy

Patient No.	Before operation	After operation					
		1 hr	*3 hr*	*1 day**	*2 days*†*	*3 days†*	*4 days*
1	0	0	0	1.6	3.4	3.9	3.7
2	0	0	0	0.9	2.3	2.9	2.8
3	0	0	0	0.9	1.9	4.0	4.5
4	0	0	0	0.7	1.5	2.1	2.1
5	0	0	0	0.9	2.3	3.6	4.1
Mean ± SE				1.0 ± 0.3	2.3 ± 0.7	3.3 ± 0.8	3.4 ± 0.9

*p = 0.033.
†p = 0.032.

Laboratory Products Inc., Clifton, New Jersey) of plasma (1 ml) was mixed with ethyl alcohol (95%, 5 ml), and heated (37° C, 3 hours). The resulting precipitate (600 × g) was resuspended (in 2 ml of water) for incubation with the anthrone reagent (10 ml, 100° C, 13 minutes). Colorimetric determinations were made at 620 nm wavelength with dextran standards prepared in an identical manner.

Tests for statistical significance were performed by the Student *t* test.

Results

Serum dextran levels were undectable (<1 mg/ml) in all patients until the 24-hour postoperative determination (Table I). Thereafter they increased in all patients through the 48-hour postoperative determination (1.0 ± 0.3 mg/ml versus 2.3 ± 0.7 mg/ml for 24- and 48-hour determinations, respectively, $p < 0.05$). Maximal plasma concentrations were found 4 days after the laparotomy (3.4 ± 0.9 mg/ml, $p < 0.01$).

By the second postoperative day, clinically significant ascites was present in all patients, which persisted until hospital discharge (day 5). All patients had spontaneous resolution of the ascites by the first clinic visit 4 weeks after surgery. No patient had an untoward side effect, and all recovered in a routine fashion.

Comment

These results demonstrate a slow resorption of dextran 70 from the peritoneal cavity evidenced by no detectable dextran in the plasma 3 hours after operation. Further, plasma dextran concentrations continued to rise through 4 days after operation. That these increasing concentrations reflect slow peritoneal resorption rather than serum build up caused by decreased renal clearance is supported by results of previous studies reporting rapid clearance (1000 gm/L) in patients with normal renal function.[2] Thus the ascites that occurs in patients with intraperitoneal instillation of dextran 70 probably is due to the physiologic third spacing of fluid in response to the persistent osmotic load.

Although the mechanism of action of dextran 70 in adhesion prevention is unknown, clinical observation of adhesion reduction in dependent areas of the pelvis[1] suggest that effects of dextran on local tissues are important. These effects simply may be mechanical displacement of pelvic viscera, enhancement of fibrinolysis, or other unrecognized activities. As inferred from the results reported here, persistence of dextran in the pelvis and the subsequent development of ascites do appear to be important in the prevention of postsurgical adhesions.

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Pregnancy complicated by solid-papillary epithelial tumor of the pancreas, pulmonary embolism, and pulmonary embolectomy

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Presented in this report is a pregnancy that was complicated by solid-papillary epithelial tumor of the pancreas, pulmonary embolism, and pulmonary embolectomy. (AM J OBSTET GYNECOL 1985;152:80-1.)

Key words: Pregnancy, solid-papillary epithelial tumor, pancreas, pulmonary embolectomy

The case that we are reporting is interesting in two respects. To the best of our knowledge, it is the first description of a solid-papillary epithelial tumor of the pancreas in a pregnant woman. In addition, it is only the fourth report of pulmonary embolectomy performed in pregnancy.

Case report

A 35-year-old Filipino woman, gravida 4, para 2-0-1-2, made her first prenatal visit at 13 weeks' gestation. The patient was completely asymptomatic, but physical examination demonstrated a large, firm, nodular mass that occupied the entire right upper quadrant of the abdomen. Sonography confirmed the presence of a large solid mass that appeared to arise from the right lobe of the liver. Standard tests of liver function were normal. Hepatitis B surface antigen and amebic and echinococcal serologies were negative. Serum α-fetoprotein and amylase levels were normal. Stool was negative for ova and parasites. Pelvic ultrasound showed a normal intrauterine pregnancy and no evidence of concurrent molar pregnancy.

Thin-needle biopsy of the mass demonstrated atypical epithelial cells and fragments of necrotic tissue. No hepatic cells were visible on histologic examination. The patient experienced intraperitoneal bleeding after this procedure and required transfusion with two units of packed red blood cells. Open biopsy subsequently showed that the large mass originated from the pancreas rather than the liver. The tumor was identified as a solid-papillary epithelial neoplasm (Fig. 1).

Two days postoperatively the patient suddenly became diaphoretic, disoriented, tachypneic, and hypotensive. Physical examination showed moderate abdominal distention, and a diagnosis of intra-abdominal bleeding was made. At exploratory laparotomy, however, there was no evidence of active internal bleeding. During the operation the patient remained in frank shock and required continuous dopamine infusion to support arterial pressure. In addition, she began to display evidence of severe pulmonary hypertension, right heart failure, and refractory hypoxemia. Pulmonary angiography showed large thrombi in the proximal portions of the right and left pulmonary arteries.

Administration of intravenous heparin solution was initiated, and the patient was maintained on mechanical ventilation. Right heart failure worsened, however, and cardiac output decreased to <2 L/min. Thoracotomy and cardiac bypass were performed, and three large thrombi were removed from the right and left pulmonary arteries. The patient's hemodynamic status improved dramatically at the conclusion of the procedure. Histologic examination of the thombi showed no evidence of tumor emboli.

Eight hours after the operation, the patient experienced spontaneous abortion of a 14-week fetus. Three weeks after embolectomy, a Whipple procedure was performed, and the pancreatic tumor was successfully removed. The patient's postoperative course was uneventful.

Comment

Solid-papillary epithelial neoplasms of the pancreas are extremely rare. Fewer than 80 cases have been reported in the literature; to date, none have occurred in association with pregnancy.[1,2] The tumors occur predominately in young women and usually originate from the tail of the pancreas. They are large, encapsulated, and hemorrhagic. Clinical manifestations typically include an enlarging abdominal mass and progressively worsening abdominal pain, but some patients, as reported here, are asymptomatic.

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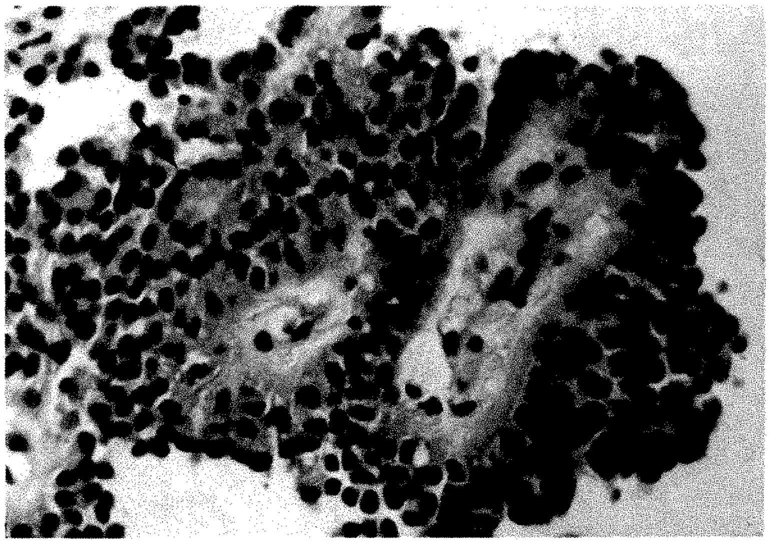

Fig. 1. High-power (×40) view of solid-papillary epithelial tumor of the pancreas demonstrates cuboidal-to-columnar cells arranged in rosettes *(arrow)* and ribbons with areas of necrosis and hemorrhage. (Hematoxylin and eosin stain.)

In light-microscopy sections, tumor cells are arranged in a papillary pattern and in pseudorosettes and ribbons (Fig. 1).[1, 2] The cuboidal-to-columnar epithelial cells have prominent eosinophilic cytoplasm. Electron microscopy studies suggest that the neoplasm originates from epithelial cells lining the small pancreatic ducts.[1] Biologically these tumors behave as low-grade malignancies; they invade contiguous structures but rarely metastasize. In a series of 52 patients reviewed by Compango et al.[1] only one individual died as a result of metastatic disease. Complete surgical resection appears to be curative.

In addition to the interesting histology of the tumor, the other unusual feature of this case was the surgical management of massive pulmonary embolism. Pulmonary embolectomy has been performed in only three other pregnant patients.[3] All three mothers and two fetuses survived. The third fetus (at 10 weeks' gestation) aborted 5 days postoperatively.

In our patient the correct diagnosis was delayed initially because of physical findings suggestive of intra-abdominal bleeding. Hemodynamic monitoring with a pulmonary artery balloon flotation catheter subsequently demonstrated acute pulmonary hypertension and right ventricular failure, thus supporting the diagnosis of acute pulmonary embolism. Pulmonary angiography was invaluable in demonstrating that the thrombi were accessible to surgical removal.

Heparin therapy alone was unsuccessful in reversing the hemodynamic derangements precipitated by massive pulmonary embolization. Fibrinolytic therapy was not considered for two reasons. The safety of fibrinolytic agents in pregnancy has not been established. In addition, our patient had an absolute contraindication to such treatment because of her three recent surgical procedures. The successful maternal outcome in this case confirms that embolectomy can be a life-saving measure when right heart failure because of massive pulmonary embolism proves refractory to conventional medical management.

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Elevated maternal α-fetoprotein levels with subsequent fetal exsanguination

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Presented is a case with persistently elevated maternal serum α-fetoprotein and normal amniotic fluid α-fetoprotein values associated with subsequent fetal-maternal bleeding and fetal death. Fetal-maternal bleeding, with potential for rhesus sensitization and fetal death, should be considered in the presence of elevated serum α-fetoprotein levels. (Am J Obstet Gynecol 1985;152:82-3.)

Key words: α-Fetoprotein, fetal exsanguination

Maternal serum α-fetoprotein evaluation has been shown to be an effective screening technique for the antenatal detection of open neural tube defects. Maternal serum α-fetoprotein has also been elevated in association with fetal abdominal wall defects, congenital nephrosis, multiple pregnancies, and abdominal pregnancies, as well as with some apparently normal fetuses. These "normal" fetuses are at increased risk for stillbirth for reasons that have not been clearly identified. The following case is reported because of the unusual association of an elevation of maternal serum α-fetoprotein with subsequent fetal death 14 weeks later caused by spontaneous major fetal-maternal hemorrhage.

Case report

The patient was a 25-year-old primiparous woman with an uncomplicated obstetric history. A routine maternal serum α-fetoprotein screening for neural tube defects at 15 weeks' gestation showed an elevated value of 153 ng/ml (mean +5 SD = 110 ng/ml). A second sample 2 weeks later was similarly elevated. A comprehensive real-time ultrasonic scan at 18 weeks' gestation failed to reveal structural anomalies. The patient was offered and accepted the use of amniocentesis for determination of amniotic fluid α-fetoprotein, which was normal at 3.95 μg/ml (mean +5 SD = 26.75 μg/ml). A third maternal serum α-fetoprotein level prior to amniocentesis at 19 weeks' gestation was markedly elevated at 762 ng/ml (mean +5 SD = 167 ng/ml).

The pregnancy proceeded uneventfully until the patient presented at 29 weeks' gestation, complaining of the abrupt cessation of fetal movements for 24 hours. Real-time ultrasonic scanner confirmed the clinical suspicion of fetal death. The patient denied having vaginal bleeding or abdominal trauma. The fetal growth had been normal and the fetus had been active until the cessation of movement. A sample of maternal blood was evaluated for evidence of fetal-maternal hemorrhage by means of the Kleihauer-Betke technique. The test suggested a fetal-maternal hemorrhage of 45 to 60 ml, estimated to represent over 50% of the circulating fetal blood volume. Maternal serum α-fetoprotein drawn after documentation of fetal death and before labor was 575 ng/ml. Limited data from our laboratory on 29-week pregnancies suggest this value is markedly elevated (mean +5 SD = 317 ng/ml). The patient was delivered of a 1320 gm stillborn male fetus without maceration with the use of prostaglandin E_2 suppositories. The placenta was removed manually with considerable difficulty because the placenta was quite adherent in some areas. A fetal blood sample could not be obtained. The fetus was grossly normal and autopsy was declined. The mother's blood type was A, Rh positive, as confirmed in early pregnancy.

Comment

The British have had considerable experience using maternal serum α-fetoprotein as a screening test for neural tube defects. Although about 90% of neural tube defects may be detected by means of this screening technique,[1] many patients identified as having an increased maternal serum α-fetoprotein level with accurate dating and single viable pregnancy will have no identifiable cause for the elevated α-fetoprotein value. Fetal blood contains much higher levels of α-fetoprotein than the mother. The case presented above is an example of a pregnancy associated with markedly elevated maternal serum α-fetoprotein values at 15, 17, and 19 weeks of gestation. Ultrasonic scan and amnio-

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centesis for α-fetoprotein gave normal results. Fetal death was documented at 29 weeks in association with a major fetal-maternal hemorrhage.

The elevation of serum α-fetoprotein in this case may have been due to a small amount of fetal-maternal hemorrhage, which remained stable until the terminal bleeding that led to fetal death. It seems reasonable to screen the maternal blood periodically in these patients to detect evidence of major bleeding and, if found, more intense evaluation and possible delivery. Prout[2] has recently reported a positive oxytocin challenge test with evidence of major fetal-maternal bleeding. This group of patients at increased risk of fetal loss from unknown causes deserves close screening and more intense study.

Although this patient was Rh positive, it seems reasonable to consider prophylactic Rh immune globulin in unsensitized Rh negative women who have an elevated maternal serum α-fetoprotein level, normal ultrasound scan, and Rh positive partner. The Rh immune globulin should be given as soon as possible with ultrasound evaluation conducted expeditiously. It is recognized there will be a delay between the serum α-fetoprotein screening and the report of the elevated level of α-fetoprotein. Elevated α-fetoprotein values are reported to the referring physician within a week in our area.

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Antenatal therapy with corticosteroids and postpartum complications

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In a group of patients receiving dexamethasone antenataly, there was no difference in incidence of postpartum complications when compared to a group treated with a placebo. It is concluded that, from the maternal point of view, selected pregnant patients may safely receive corticosteroids to minimize the incidence of respiratory distress syndrome. (Am J Obstet Gynecol 1985;152:83-4.)

Key words: Dexamethasone, respiratory distress syndrome, postpartum complications

The antenatal administration of certain corticosteroids has been shown to be of value in reducing the incidence of neonatal respiratory distress syndrome (RDS).[1] However, some investigators have raised concern about possible adverse effects of such therapy.[2]

The recently completed collaborative study on the prevention of RDS by antenatal administration of dexamethasone[1] provided data that have been used to help clarify the issue of risk versus benefit in the antenatal use of corticosteroids.

The experimental design of the collaborative study on the effect of antenatal dexamethasone administration on the prevention of RDS has been described in detail.[1] Briefly 696 women between 26 and 37 weeks' gestation were randomized into a placebo or treatment group. The steroid group received up to 20 mg of dexamethasone intramuscularly in four divided doses every 12 hours while subjects in the placebo group received an inert vehicle which appeared identical to the study drug. The diagnosis of RDS was determined by use of well-defined criteria.[1]

In this report we have compared 336 patients in the control group and 342 patients in the treatment group regarding the incidence of the following postpartum complications: intrauterine, episiotomy, and wound infections, hypertension, gastrointestinal bleeding, and hypersensitivity reactions. Eighteen mothers were lost to the study prior to the delivery or before postpartum

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Table I. Comparison of treatment groups by postpartum complications during hospital stay

Complication	*Treatment (% with complication)*		
	Placebo	*Steroid*	*p Value*
Intrauterine infections	7.1 (24*)	7.5 (26)	0.82
Episiotomy infection	0	0	–
Wound infection	1.5 (5)	1.2 (7)	0.58
De novo hypertension†	0.3 (1)	1.0 (3)	0.62
Aggravation of preexisting hypertension‡	8.7 (4)	13.3 (6)	0.49
Gastrointestinal bleeding	0	0	–
Hypersensitivity reactions	0.6 (2)	0	0.25

*The numbers in parentheses are the number of cases. The denominators for the percentages are 336 for the placebo group and 342 for the steroid group.

†The denominator for the percentages is the number of cases without pregnancy-induced or chronic hypertension (290 in the placebo group and 297 in the steroid group).

‡The denominator for the percentages is the number of cases with pregnancy-induced or chronic hypertension (46 in the placebo group and 45 in the steroid group).

data could be ascertained. There were 46 mothers in the placebo group and 45 in the steroid group with chronic hypertension or pregnancy-induced hypertension. The rates of aggravation of preexisting hypertension were calculated only within this group of women. The rate of de novo hypertension was calculated among those women who did not have chronic or pregnancy-induced hypertension (290 in the placebo group and 297 in the steroid group).

The data were analyzed with the use of the χ^2 test or Fisher's exact test as was appropriate.

The results of the analyses shown in Table I indicate that there were no significant differences between the placebo and the steroid-treated groups in the incidence of the complications analyzed.

It is clear that when a large number of patients treated antenatally with dexamethasone was compared to placebo-treated patients there was no difference in incidence of uterine, episiotomy, or cesarean wound infection. These findings are not in agreement with those of Taeusch et al.[2] who found an increased incidence of maternal infectious morbidity in mothers with ruptured membranes for >48 hours and who received dexamethasone therapy. The incidence of premature rupture of the membranes in our population was not different between the placebo group and the dexamethasone group[1] while in the study of Taeusch et al. there was a difference. Furthermore the latter study had only 10 patients in the steroid group and 17 in the placebo group with ruptured membranes >48 hours. The facts that our randomization produced no bias as far as premature rupture of the membranes and that our sample size was considerably larger provide considerable support to our findings.

Lastly, there was no effect of steroid therapy on maternal blood pressure or on gastrointestinal vascular stability. Thus these results demonstrate that there are no adverse maternal effects of antenatal dexamethasone therapy so that from the maternal point of view properly selected pregnant women may safely receive corticosteroid therapy in an effort to minimize the incidence of neonatal RDS.

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WARNING:

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. OGEN SHOULD NOT BE USED DURING PREGNANCY.

According to some investigators, the use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. Studies have reported that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] In one of these studies, this risk was estimated as not greater than 4 per 1000 exposures.[7] Furthermore, there are reports that a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these reported changes are histologically benign, the investigators have not determined whether they are precursors of adenocarcinoma.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies in the offspring, including heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. OGEN has not been studied for these uses, and therefore should not be used during pregnancy. There is no evidence from well controlled studies that progestogens are effective for these uses.

If OGEN (estropipate tablets) is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the question of continuation of the pregnancy should be addressed.

INDICATIONS

OGEN (estropipate tablets) is indicated for the treatment of estrogen deficiency associated with:

1. Moderate to severe *vasomotor* symptoms of menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.

OGEN (ESTROPIPATE TABLETS) HAS NOT BEEN TESTED FOR EFFICACY FOR ANY PURPOSE DURING PREGNANCY. SINCE ITS EFFECT UPON THE FETUS IS UNKNOWN, IT CANNOT BE RECOMMENDED FOR ANY CONDITION DURING PREGNANCY (SEE BOXED WARNING).

CONTRAINDICATIONS

OGEN should not be used in women with any of the following conditions:

1. Known or suspected cancer of the breast.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (See Boxed Warning).
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use.

WARNINGS

1. *Induction of malignant neoplasms.* Long-term continuous administration of natural and synthetic estrogens in certain animal species has been reported by some investigators to increase the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning).

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent long-term followup of a single physician's practice has raised this possibility.[18] Therefore, caution should be exercised when administering estrogens to women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. Careful breast examinations should be performed periodically.

2. *Gall bladder disease.* A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens,[17] similar to the 2-fold increase previously noted in users of oral contraceptives.[19,22] In the case of oral contraceptives, the increased risk appeared after two years of use.[22]

3. *Effects similar to those caused by estrogen-progestogen oral contraceptives.* There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat postpartum breast engorgement would be more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in women receiving estrogens for postpartum breast engorgement.[20,21]

a. *Thromboembolic disease.* It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[22-29] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.[30,31] An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives.[32,33] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism; it should also be discontinued during periods of prolonged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found[17,34] this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk. Therefore estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

b. *Hepatic adenoma.* Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[36-38] Although benign, and rare, these may rupture and cause death through intraabdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[37] The relationship of this malignancy to these drugs is not known at this time.

c. *Elevated blood pressure.* Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with use of estrogens in the menopause[39] and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. *Glucose tolerance.* A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

4. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS

A. General Precautions.

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

2. Fluid retention — Estrogens may cause some degree of fluid retention. Therefore, patients with conditions such as epilepsy, migraine, and cardiac or renal dysfunction, which might be influenced by this factor, require careful observation.

3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression.[22] Although it is not clear whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size during estrogen use.

6. The pathologist should be advised of the patient's use of estrogen therapy when relevant specimens are submitted.

7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen.

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

B. Information for the Patient. See text of Patient Package Insert which appears after PHYSICIAN REFERENCES.

C. OGEN (estropipate tablets) cannott be recommended for use during pregnancy. See Contraindications and Boxed Warning.

D. Nursing Mothers. Estrogens have been reported to be excreted in human breast milk.

ADVERSE REACTIONS

(See Warnings regarding reports of possible induction of neoplasia, unknown effects upon the fetus, increased incidence of gall bladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

1. *Genitourinary system.*
Breakthrough bleeding, spotting, change in menstrual flow.
Dysmenorrhea.
Premenstrual-like syndrome.
Amenorrhea during and after treatment.
Increase in size of uterine fibromyomata.
Vaginal candidiasis.
Change in cervical eversion and in degree of cervical secretion.
Cystitis-like syndrome.

2. *Breast.*
Tenderness, enlargement, secretion.

3. *Gastrointestinal.*
Nausea, vomiting.
Abdominal cramps, bloating.
Cholestatic jaundice.

4. *Skin.*
Chloasma or melasma which may persist when drug is discontinued.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Loss of scalp hair.
Hirsutism.

5. *Eyes.*
Steepening of corneal curvature.
Intolerance to contact lenses.

6. *CNS.*
Headache, migraine, dizziness.
Mental depression.
Chorea.

7. *Miscellaneous.*
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria.
Edema.
Changes in libido.

ACUTE OVERDOSAGE

Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that serious ill effects do not occur. Overdosage of estrogen may cause nausea and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

1. *Given cyclically for short-term use:*

For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., 3 weeks on and 1 week off).

Attempts to discontinue or taper medication should be made at 3 to 6 month intervals.

The usual dosage range is one OGEN .625 (estropipate) Tablet to one OGEN 5 Tablet per day.

2. *Given cyclically:*

Female hypogonadism. Female castration. Primary ovarian failure. The lowest dose that will control symptoms should be chosen. A daily dose of one OGEN 1.25 Tablet to three OGEN 2.5 Tablets may be given for the first three weeks of a theoretical cycle, followed by a rest period of eight to ten days. The same schedule is repeated if bleeding does not occur by the end of the rest period. The duration of cyclic estrogen therapy necessary to produce withdrawal bleeding will vary according to the responsiveness of the endometrium. If satisfactory withdrawal bleeding does not occur, an oral progestogen may be given in addition to estrogen during the third week of the cycle.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

OGEN (estropipate tablets, USP) is supplied as OGEN .625 (0.75 mg estropipate), yellow tablets, **NDC** 0074-3943-04; OGEN 1.25 (1.5 mg estropipate), peach-colored tablets, **NDC** 0074-3946-04; OGEN 2.5 (3 mg estropipate), blue tablets, **NDC** 0074-3951-04; and OGEN 5 (6 mg estropipate), light green tablets, **NDC** 0074-3958-13. Tablets of all four dosage levels are standardized to provide uniform estrone activity and are grooved (Divide-Tab®) to provide dosage flexibility. All tablet sizes of OGEN are available in bottles of 100.

5043716

Abbott Laboratories
Abbott Pharmaceuticals, Inc.
North Chicago, Illinois 60064

A Near-Spotless Record.

Other OCs claim it. We show it.[1]*

In clinical trials, Lo/Ovral was practically perfect in holding spotting and breakthrough bleeding to a minimum.[†]

	SPOTTING	BREAKTHROUGH BLEEDING
Cycle 1	10.6%	8.8%
Cycle 3	6.3%	3.3%
Total Cycles[‡]	4.2%	2.9%

Lo/Ovral® offers less breakthrough bleeding and spotting, along with high contraceptive efficacy, at a low dose—just 30 mcg ethinyl estradiol and 0.3 mg norgestrel.

LOW DOSE

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth.

[1] Dickey RP: Managing Contraceptive Pill Patients, 3rd ed., Durant, Oklahoma, Creative Infomatics, Inc., 1983.

[*] Rates are derived from separate studies from different investigators in several population groups and cannot be compared precisely.

[†] Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives.

[‡] Data on file for 22,489 total cycles, Wyeth Laboratories. **See important information on following page.**

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions:

1. Thrombophlebitis or thromboembolic disorders.
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders.
3. Cerebral-vascular or coronary-artery disease.
4. Known or suspected carcinoma of the breast.
5. Known or suspected estrogen-dependent neoplasia.
6. Undiagnosed abnormal genital bleeding.
7. Known or suspected pregnancy (see Warning No. 5).
8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

PERSISTENCE OF RISK OF VASCULAR DISORDERS—Findings from one study in Britain involving cerebrovascular disease and another in the U.S. concerning MI suggest an increased risk of these conditions in users of OC's persists after discontinuation of the OC's. In the British study, risk of cerebrovascular disease remained elevated in former OC users for at least 6 years after discontinuation. In the U.S. study, increased risk of MI persisted for at least 9 years in women 40 to 49 years old who had used OC's for 5 or more years. Findings in both studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind.

In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests.

As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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LO/OVRAL® each tablet contains
0.3 mg norgestrel with
0.03 mg ethinyl estradiol.

Wyeth Laboratories
Philadelphia, PA 19101

An arteriovenous malformation in pregnancy: A case report and review of the literature

James A. Elliott, M.D., Richard N. Rankin, M.D., Martin J. Inwood, M.D., and J. Kenneth Milne, M.D.
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A case is described of a young woman with progression of a macrofistulous arteriovenous malformation during pregnancy. This resulted in severe symptoms necessitating cesarean section, following which there was a dramatic postpartum recovery. The arteriovenous malformation was confirmed by angiography. The literature related to arteriovenous malformations in pregnancy is reviewed. (AM J OBSTET GYNECOL 1985;152:85-8.)

Key words: Arteriovenous malformations, pregnancy

Pregnancy can have a marked adverse effect on vascular malformations which can result in serious complications. An unusual case of a young woman is described which illustrates this phenomenon. Following this is a review of the literature pertaining to vascular malformations in pregnancy.

Case report

The patient was a 28-year-old woman, gravida 2, para 0, who presented at 18 weeks' gestation with a 2-week history of increasing swelling, pain, and cyanosis of the left arm. The only relevant previous history was a congenital port wine stain and long-standing slight enlargement of the left hand. Initially, thrombosis of the axillary vein was considered possible and the patient was treated with heparin for 6 days. At that time, Doppler examination with a nondirectional Doppler unit (Bach-Simpson, Model BVM-315, 5 MHz probe) showed increased arterial flow in the hand and increased venous pressure in the arm (60 mm Hg compared with 20 mm Hg on the right), and the diagnosis of an arteriovenous malformation of the left hand was made and subsequently confirmed. Partial venous occlusion, possibly due to extrinsic compression at the axillary or subclavian level, was suspected as the cause of arm swelling. The patient was discharged but readmitted at 22 weeks' gestation with increasing pain and swelling of the left arm, as well as shortness of breath, palpitations, pounding headache, and light-headedness. Doppler findings were essentially unchanged. No pressures were recorded as the arm was painful to touch, and waveform data were not obtained. Heart rate was 100 to 130/bpm with an S3-S4 gallop, and marked left ventricular heave. Two-dimensional echocardiography showed left ventricular hypertrophy with an estimated cardiac output of greater than 8 L/min. Dyspnea at rest was present and bibasal râles were heard on auscultation. The diagnosis of congestive heart failure was made and she was started on a regimen of digoxin, with an excellent clinical response. There was no clinical evidence to suggest a pulmonary embolus.

The hemoglobin at that time was 89.0 gm/L, and a transfusion was given. Reticulocyte count was increased to 235.0 × 10^9/L, bilirubin rose from 8.0 to 23.0 μmol/L with a change in haptoglobin level to <50 μmol/L. Hemosiderin was also demonstrated in the urine. This was therefore considered to be a fragmentary hemolytic anemia and was treated by transfusion and oral iron administration.

The subsequent course in the hospital was characterized by relentless and increasing pain and ischemic changes with ulceration of the tip of the left middle finger and atrophy of the muscles of the left hand (Fig. 1). A variety of attempts were made to control the pain including acupuncture, biofeedback, various nonnarcotic medications, and compressive wrappings. However at 32 weeks' gestation a cesarean section was performed because of relentless pain and fear for the viability of the patient's left hand. A male infant was born who, after initial problems with respiratory distress syndrome, has done well. Coincidentally, the baby had a congenital cavernous hemangioma on his back at birth.

Following the delivery there was a dramatic improvement in the condition of the patient's hand within the first few days. This improvement continued at a slower rate over the next few months.

An angiogram was obtained approximately 2½ weeks post partum. The plain film showed marked osteoporosis of the hand (Fig. 2). The angiogram revealed a large macrofistulous arteriovenous malformation on the dorsum of the left hand including the three fingers on the ulnar side (Fig. 3). Proximal vasculature of the arm was normal.

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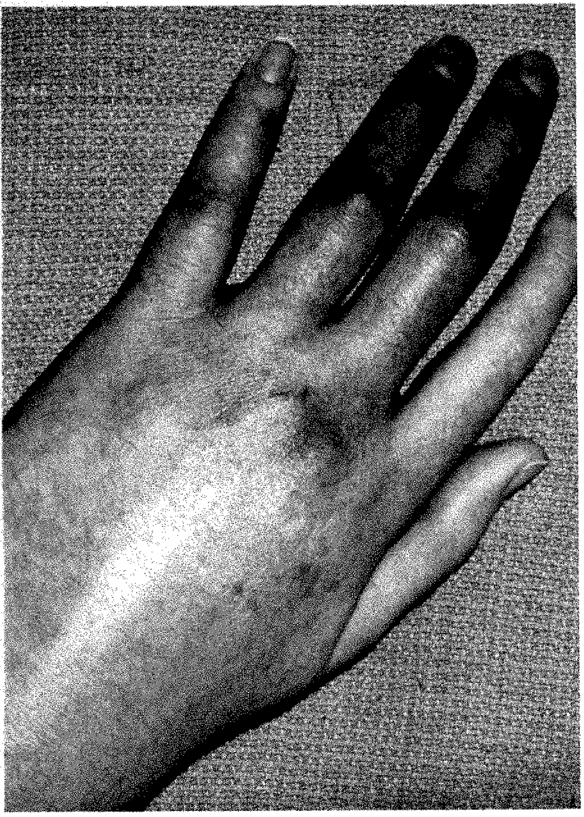

Fig. 1. Clinical picture of the left hand, taken during the last trimester of pregnancy. Note the marked swelling with ischemic ulceration of the tip of the left middle finger.

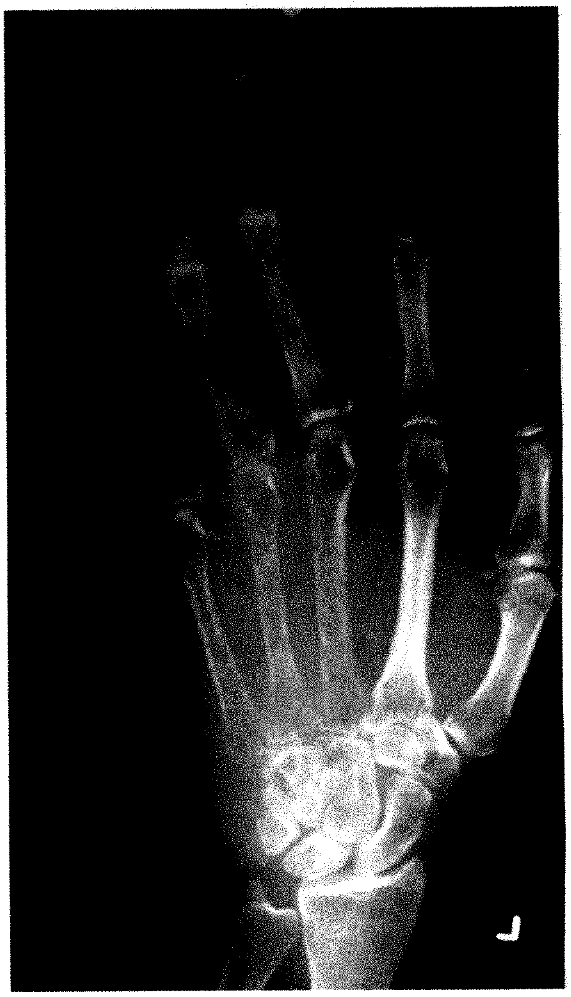

Fig. 2. Anteroposterior view of left hand. Note the marked osteoporosis involving primarily the ulnar three rays of the hand.

Because of the continued slow spontaneous improvement the patient was treated conservatively. At the present time the patient experiences only mild discomfort and swelling of the left hand in hot weather and has regained full use of the hand with the exception of mild extension contractures of the fingers.

Comment

The subject of vascular malformations is confused by the large numbers of different names used for these lesions. These include capillary and cavernous hemangiomas, port wine stains, circoid, racemose, or serpentine aneurysms, congenital arteriovenous malformations, fistulas, aneurysms, and communications. This probably results because of the wide spectrum of clinical, pathologic, and angiographic manifestations which can occur with these lesions.

Szilagyi et al.[1] believe that these are anomalies which occur as a result of arrest or misdirection of development of the primitive vascular system. They propose the classification of congenital arteriovenous communications based on correlation of the clinical and angiographic findings with the stage of embryologic development at which the lesions were felt to occur. They divide these into four categories: (1) hemangiomas, (2) microfistulous arteriovenous aneurysms, (3) macrofistulous arteriovenous aneurysms, and (4) anomalous mature vascular channels. Hemangiomas occur at the earliest stage and the others occur at progressively later stages.

More recently Mulliken and Glowacki[2] have attempted to further simplify the situation by dividing these vascular lesions into two major groups, hemangiomas and vascular malformations, based on histopathologic studies. They believe that hemangiomas are actually benign neoplasms which show increased mitotic activity and which go through a proliferating and involuting phase. However, vascular malformations are errors of morphogenesis with stable cellularity. These are present at birth and grow commensurately with the child although they can be influenced by hormonal balance and other factors affecting blood flow. These vascular malformations can be composed of any combination of capillary, arterial, venous, or lymphatic components and may or may not have fistulas. The authors included port wine stains in this latter category. In the present case the patient had a port wine stain which likely contained a long-standing fistulous component which would explain the slight enlargement of the left hand. These fistulas progressed during pregnancy and became grossly macrofistulous, resulting in congestive heart failure and a mechanical fragmentary hemolytic anemia. The arteriovenous shunt also resulted in ischemic changes distally likely due to underperfusion of the normal capillary network distal to the shunt. The localized osteoporosis is likely due to the marked hyperemia in the hand caused by the arteriovenous malformation.

Review of the literature reveals rather scanty material regarding vascular malformations in pregnancy. However, there are several case reports of both the development of new lesions and the progression of preexisting lesions during pregnancy. There are also a few reports relating changes in vascular malformations to the menarche and menses.

There are 11 case reports of cutaneous hemangiomas which initially developed during pregnancy.[3, 4] These were all capillary or cavernous hemangiomas which appeared at various locations including the hands, wrists, lips, and tongue. Three of these showed some spontaneous postpartum regression. In two patients the lesion progressed in subsequent pregnancies. In addition, there are four case reports in which a preexisting cutaneous hemangioma showed progression during pregnancy.[3-5] These were hemangiomas of the lip, face, and neck.

There are also two case reports of patients with cutaneous hemangiomas who noticed changes at menarche or related to the menstrual cycle. Folin, in 1861, described a woman with a hemangioma of the lip which was influenced by menstruation and grew during pregnancy.[4] Owen[6] described a patient with a hemangioma on the face which grew rapidly after menarche and became painful regularly during the menstrual cycle.

There are a number of case reports of pelvic arteriovenous malformations complicating pregnancy. Benson et al.[7] reported on three patients who presented with pelvic pain beginning or increasing in pregnancy, one of whom had an extensive arteriovenous malformation involving the pelvis and right knee.

There are also a number of reports of spinal vascular malformations which presented with neurological symptoms during pregnancy.[8-12] Of a total of 13 cases, nine showed some spontaneous improvement post partum. One of these patients died of heart failure prior to delivery in her ninth pregnancy.[9] In another four cases operation was required in the postpartum period or at a later time.[9, 10] Three patients required decompressive surgical procedures during pregnancy.[9-11]

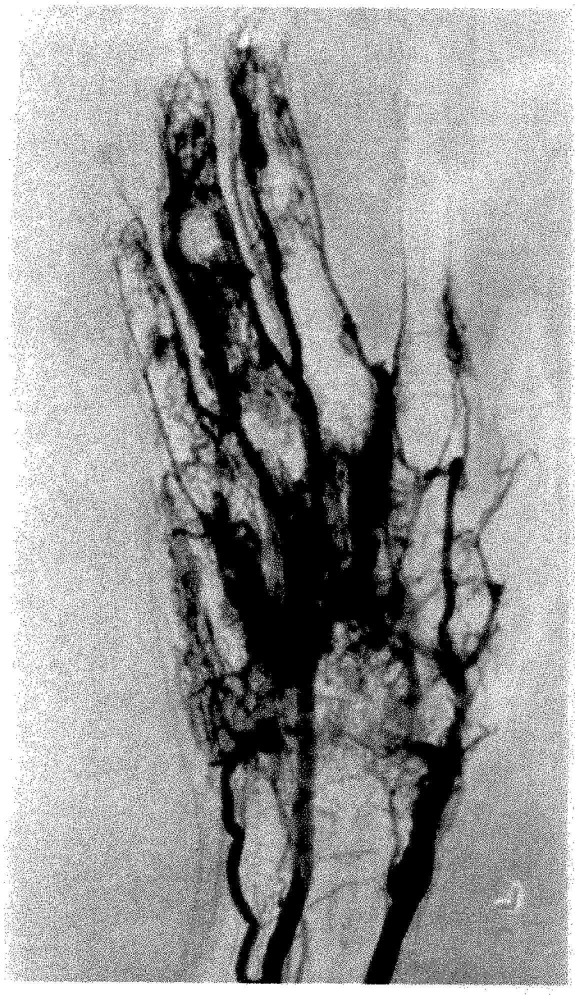

Fig. 3. Arteriogram of the left hand 2½ weeks post partum. There is a macrofistulous arteriovenous malformation involving the dorsum of the left hand and the ulnar three fingers. Marked arteriovenous shunting is present.

Cerebral arteriovenous fistulas in pregnancy have also been described. Carotid-cavernous fistulas in pregnancy are not rare according to Raskin et al.[13] Most of these are now felt to be a type of dural arteriovenous fistula.[14] Walker and Allegre[15] stated that 25% to 30% of women with carotid-cavernous fistulas develop them during pregnancy or delivery. Toya et al.[14] cited Sattler (from 1920), who found that 17 of 41 spontaneous carotid-cavernous fistulas occurred during pregnancy. However, angiographically proved cases of carotid-cavernous fistulas developing in pregnancy and the early postpartum period are few. Toya et al.[14] found only five reported cases. They added two cases of their own which were proved dural arteriovenous fistulas. Both of these showed clinical improvement at the termination of pregnancy and in one there was angiographic proof of disappearance of the carotid-cavernous fistulas.

There is also an association between cerebral arteriovenous malformations and pregnancy. Robinson et al.[16] reported on a large group of patients diagnosed as having either an arteriovenous malformation or an aneurysm. In the group in which the presentation was related to pregnancy, 36% of the patients had an arteriovenous malformation versus 9.3% in the group overall. Also, of the patients with arteriovenous malformations, subarachnoid hemorrhage is much more likely to occur in pregnancy, with a frequency of 87%, whereas the risk of subarachnoid hemorrhage from an arteriovenous malformation is 10% if a patient is not pregnant. From this discussion, it appears that pregnancy does influence both the development and the progression of vascular malformations. It is also clear that many of these show spontaneous postpartum regression which is often dramatic, as in the case presented. The exact reason why this is so is speculative at this time. It is certainly reasonable to postulate that the changing hormonal balance in pregnancy is responsible, but there is no definite proof that this is the case. It is known that estrogens are associated with arterial spider telangiectasias[3] and that they dilate the ear veins of oophorectomized rabbits.[8] Progesterones have been linked to increased venous distensibility by McClausland et al.,[17, 18] who showed increased venous distensibility in pregnancy, during the second half of the menstrual cycle, and after castration in women given progesterones but not given estrogens. This may be related to the known phenomenon that progesterone inhibits smooth muscle.[19] The change in estrogen and progesterone status may also explain the changes seen related to menses and menarche in the cases described.

Other mechanisms may be contributing in certain cases such as obstruction of venous return from the pelvis by the enlarged uterus in the case of pelvic arteriovenous malformations. The effects exerted by the general expansion of blood volume and the cardiovascular changes which occur during pregnancy are also speculative.

There are a few diagnostic and therapeutic lessons to be gained from this case report and the literature review. First, all patients with a port wine stain or a known arteriovenous malformation should be carefully monitored throughout pregnancy for potential complications, both local (ischemia) and systemic (cardiac failure). Second, a noninvasive method of initial diagnosis and follow-up is available in the use of Doppler ultrasound, which should be used in preference to standard radiologic techniques to avoid ionizing radiation during the pregnancy. Third, if at all possible, obliterative therapy for the arteriovenous malformation should be delayed until the postpartum period as spontaneous regression may occur.

In summary, it is clear that pregnancy can have a marked adverse effect on vascular malformations. Fortunately, such effects appear to be uncommon and very rarely as severe as they were in the patient presented.

The help of Dr. F. N. McKenzie in the treatment of this patient and in the preparation of the manuscript is acknowledged.

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Aminoglycoside dosing in obese puerperal women

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We compared serum aminoglycoside levels in two groups of obese puerperal women being treated for endometritis. In these obese puerperal women (weights as much as 100 kg), the aminoglycoside dose did not have to be adjusted for excess weight initially, but it seems that determination of antibiotic levels should be performed in view of the large doses. (AM J OBSTET GYNECOL 1985;152:89-90.)

Key words: Aminoglycoside, endometritis, obesity, puerperium

After standard doses of gentamicin and tobramycin, serum levels of these antibiotics are often low in puerperal women, most likely because of a larger volume of distribution (mainly extracellular fluid) and more rapid renal clearance.[1] On the other hand, in obese, nonpregnant subjects, blood levels are approximately 25% higher than in nonobese subjects.[2] Because obesity and pregnancy often occur simultaneously, we compared serum aminoglycoside levels in two groups of obese, puerperal women being treated for endometritis. One group received an adjusted dose of aminoglycoside as recommended for obese, nonpregnant adults.[2] This method of calculating the dose was based on lean body weight plus 40% of excess weight, to account for partial distribution of aminoglycosides to the extracellular fluid of adipose tissue. The other group received an unadjusted dose based on actual body weight. Patients were not randomized to the adjusted- or unadjusted-dose group.

These data were collected from patients participating in randomized antibiotic trials between April, 1982, and December, 1983. All of these subjects weighed more than 30% in excess of desirable weights according to weight and height tables for adult women.

The adjusted-dose group received, every 8 hours, 1.5 mg of aminoglycoside per kilogram of lean body weight plus 40% of the excess body weight times 1.5 mg. The group receiving the unadjusted dose received 1.5 mg/kg of actual body weight, up to a maximum of 150 mg every 8 hours.

The dose of aminoglycoside was infused in 100 ml diluent during a period of 30 minutes every 8 hours. Each patient also received intravenous clindamycin. On the second or third day of therapy, a blood specimen was drawn for determination of antibiotic levels 30 minutes after completion of the infusion. Trough concentrations were not routinely determined because these have been uniformly low in our patients.

Blood samples were centrifuged and serum assayed that day or frozen at −20° C and assayed within 3 days. The assay was performed with a fluorescence polarization, competitive binding immunoassay (Abbott TDX, Irving, Texas).

Each patient had pretherapy and posttherapy serum creatinine determinations performed, but none had audiometric testing. Serum levels between 5 and 10 μg/ml were considered "therapeutic." Statistical analysis was by two-tailed Student's t test.

Aminoglycoside levels were determined in 27 obese puerperal women. Thirteen received the adjusted dose (all gentamicin); 14 received the unadjusted dose (five gentamicin, nine tobramycin). There were no statistically significant differences between the adjusted- and unadjusted-dose groups for years of age (26.1 ± 7.0 versus 22.9 ± 3.6 years), weight (90.4 ± 13.5 versus 85.4 ± 8.7 kg), height (61.8 ± 2.6 versus 61.3 ± 2.2 inches), excess weight (51% ± 16% versus 46% ± 18%) or serum aminoglycoside level (4.7 ± 1.4 versus 5.5 ± 1.6 μg/ml). The adjusted-dose group did receive a lower mean dose (109 ± 16 versus 128 ± 10 mg, $p < 0.002$). No patient showed evidence of nephrotoxicity, and no level exceeded 10 μg/ml.

Recent studies have noted that one third to one half of puerperal women will have "subtherapeutic" tobramycin or gentamicin levels following administration of standard doses (3 to 5 mg/kg/day).[1] However, Schwartz et al.[2] have shown that, given a dose of 1 mg/kg of actual body weight, healthy obese adult subjects had significantly higher aminoglycoside levels (25% higher) than did subjects of normal weight. Although gentamicin and tobramycin are thought to be distributed mainly to extracellular fluid, Schwartz et al.[2] point out that fatty tissue contains about 45% to 50% of the extracellular water of nonadipose tissue (in the form of blood and interstitial fluid). Accordingly, they recom-

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mend that, for moderately obese patients (30% to 100% excess weight), aminoglycoside dosage be based on lean body weight plus 40% of the excess body weight.

Because obesity is a common complication of pregnancy in our population, we compared the peak levels in obese patients given either the adjusted or the nonadjusted dose. Several problems exist in our study. First, patients in the unadjusted-dose group all received gentamicin, whereas nine of 14 in the unadjusted-dose group received tobramycin. However, these two antibiotics have virtually identical kinetics. Second, this was not a randomized study, but we note that these two groups were similar in all aspects except for dose received. Third, because few patients were studied, small but real differences in the group characteristics or in mean antibiotic levels may not have been detected, but we believe that, clinically, these are similar groups. Further, although a larger series might demonstrate a significantly higher antibiotic level in the unadjusted-dose group, the mean of that group (5.5 ± 1.6 μg/ml) still allows a considerable margin of safety.

In obese puerperal women (as much as 100 kg), the dose of gentamicin or tobramycin need not be adjusted for excess weight initially, but determination of antibiotic levels seems appropriate in view of the large doses.

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Exercise dynamics in late gestation: Effects of physical training

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Heart rate and stroke volume were measured serially in subjects at rest in the sitting position and at the onset and end of a 6-minute period of upright bicycle exercise. Twenty-three subjects with normal pregnancy were studied in late gestation and again post partum. Rest and exercise cardiac outputs in late gestation were not different from those in the postpartum period. Heart rate was higher at rest and stroke volume lower during exercise in late gestation than post partum. At the end of exercise, stroke volume fell dramatically in late gestation but not post partum. Ten women prospectively identified as physically fit had responses that were not different from those of the nonfit cohort in late gestation. Post partum, the physically fit women had exercise responses typical of trained persons and different from those of the nonfit cohort. In late gestation, rest and exercise hemodynamics in subjects in the sitting position appeared to be dominated by factors influencing venous return, independent of physical fitness. (AM J OBSTET GYNECOL 1985;152:91-7.)

Key words: Maternal cardiac output, exercise, stroke volume, fitness, posture

Regulation of circulatory dynamics with changes in posture is challenged uniquely in humans, and the challenge is severe during late gestation when the gravid uterus impedes venous return, at least in the supine and sitting positions.[1, 2] Increased venous capacitance during gestation[3] may aggravate this mechanical obstruction. Serial studies of blood volume[4] and left ventricular volume[5] show that both increase throughout gestation. Nevertheless, rest and exercise stroke volumes in women near term, in both the supine and sitting positions, are not appreciably greater than those measured post partum.[2, 6] These seemingly conflicting data need to be explained.

The importance of the gravid uterus in restricting venous return (and therefore stroke volume) in the supine and sitting positions has been suggested by several authors.[1, 2, 6] Other possible explanations for a low exercise stroke volume during pregnancy include reduced ventricular contractility or reduced maternal fitness due to inactivity. We reasoned that measurements of maternal stroke volume at the onset and end of bicycle exercise would help elucidate the importance of venous return in late gestation. The responses of physically fit and nonfit women would address the contribution of maternal exercise history to late gestation hemodynamics. Accordingly, we investigated the response of maternal heart rate and stroke volume to upright bicycle exercise in late gestation; the data were compared with those obtained in the same women post partum.

Methods

Twenty-three women volunteered to participate in a protocol approved by the Human Research Committee of the Oregon Health Sciences University. Referrals for the protocol came from a community-based exercise class called "Fitness in Pregnancy." Women generally enter the class at 16 weeks of gestation. Isotonic exercise is performed for 30 minutes three times each week at 60% to 70% of age-predicted maximal heart rate.

Subjects were studied at 34 and 38 weeks of gestation and 12 weeks post partum. Studies were performed

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Table I. Maternal and fetal demographics

Factor	*Fit*	*Nonfit*
Age (yr)	28.3 ± 2.4	28.8 ± 1.8
Height (m)	1.66 ± 0.04	1.63 ± 0.06
Pregravid weight (kg)	54.2 ± 5.1	54.0 ± 4.6
Gestation (wk)	39.8 ± 1.8	40.5 ± 1.2
Birth weight (gm)	3286 ± 344	3316 ± 366

Mean ± 1 SD.

between 9:30 AM and noon; subjects had partaken of a light breakfast without caffeine. Data were collected with the subject sitting upright on a bicycle ergometer during rest for 6 minutes, while pedaling at a rate of 40 to 50 rpm and an exercise intensity of 300 kpm · min^{-1} for 6 minutes, and during 10 minutes of recovery. During the recovery period, pedaling was not allowed but subjects were permitted to place their feet on the motionless pedals or the ergometer yoke.

At each study session, blood pressure was recorded at one-minute intervals with an Infrasonde blood pressure monitor (Marion Scientific, Costa Mesa, California) during rest, within 15 seconds after the cessation of exercise, and at 1-minute intervals during recovery. Electrocardiogram, basilar phonocardiogram, and transthoracic dZ/dt (the derivative of electrical impedance [Z] with respect to time, in ohms per second) were recorded continuously on an Elema Schönander four-channel ink-jet recorder. To measure impedance, two mylar tapes with aluminum bands (3M Corp., Minneapolis, MN) were placed around the lower neck and two around the thorax: the outer pair transmitted a 100 kHz 2 ma current and the inner pair measured impedance. A Minnesota Impedance Cardiograph model 304B (Surcom Inc., Minneapolis, MN) was used to generate dZ/dt and measure basal transthoracic impedance. Stroke volume was calculated from the Kubichek equation as modified by Denniston et al.[7]:

$$SV = \rho \frac{Lo^2}{Zo^2} dZ/dt\ ET \qquad (1)$$

where SV = stroke volume, ρ = resistivity of blood (ohms) = $56.8e^{0.025H}$, H = hematocrit obtained from packed cell volume, Lo = shortest distance between the inner electrodes on the neck and chest (centimeters), Zo = basal impedance (ohms), dZ/dt = minimum value of the derivative of impedance with respect to time (ohms · second^{-1}), ET = ejection time (seconds).

In order to familiarize ourselves with this technique and to test its validity in our laboratory, we obtained simultaneous measurements of cardiac output by impedance cardiography and by either a direct Fick method or an indicator dilution technique in patients in the cardiac catheterization laboratory or coronary care unit. Aortic insufficiency systematically caused overestimation of cardiac output by impedance, and data from patients with aortic insufficiency were deleted from further analysis. Seventy-one pairs of outputs, 56 during rest and 15 during exercise, showed a correlation coefficient of 0.72 with a slope not different from 1. The average cardiac output by impedance was not different from the average obtained by the standard techniques. Serial measurements were made in 15 subjects during rest and exercise; in 10 subjects two measurements were made at an interval of 30 minutes and in seven subjects at an interval of 1 day. The correlation coefficient for the change in output by impedance and a standard technique was 0.73. The changes measured by impedance and standard techniques were not different from one another.

Stroke volume measurements were made at 2 and 5 minutes of rest, at 1, 3, and 5 minutes of exercise, and at 1, 3, 5, and 9 minutes of recovery. Each measurement of stroke volume was made during end-expiratory apnea and the average dZ/dt and ET during six cardiac cycles were used in equation 1. Heart rate was calculated from the six-cycle lengths and cardiac output was computed as the product of the averages of heart rate and stroke volume.

Fitness questionnaire. On entering the study, each subject completed a questionnaire detailing her exercise history prior to and during pregnancy. Women who had performed regular aerobic exercise (for instance, running, swimming) three times a week for 45 minutes each time and for at least 2 years prior to pregnancy were termed "fit"; the remainder were considered as nonfit controls.

Data analysis. The unpaired *t* test was used to compare resting and exercise values at 34 and 38 weeks of gestation. Because no differences between the two time periods were found, 34- and 38-week data were averaged thereafter. Data within rest periods were not statistically different (analysis of variance) and were therefore averaged to provide a single value. Data within exercise periods were likewise not different, but the 5-minute measurements were used to better approximate steady-state values. Recovery measurements were analyzed individually. Hemodynamic data were analyzed by pregnancy state, fitness state, and study condition (rest, exercise, and recovery intervals) by three-way analysis of variance.[8] Significant differences were then pursued by determination of simple main effects. The Newman-Keuls range test was used to determine significant changes from the resting condition.[8]

Results

Demographic data for the 23 subjects in the study group are shown on Table I. No subject had hyperten-

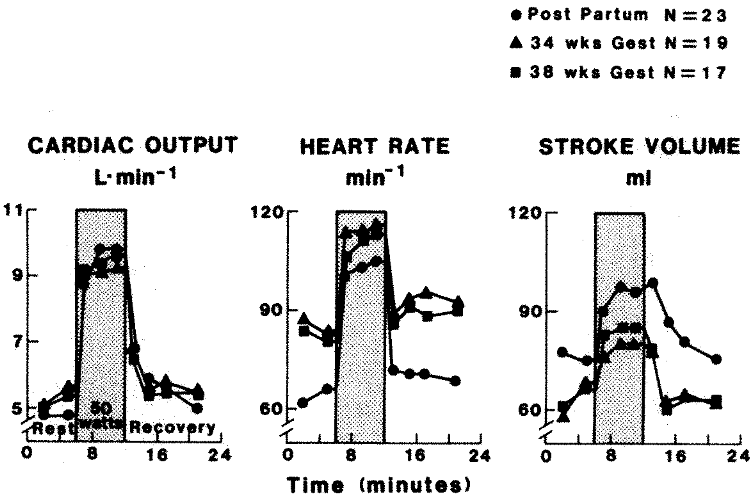

Fig. 1. Cardiac output and its components, heart rate and stroke volume, are shown at rest, during 50 W upright bicycle exercise, and during recovery at 34 and 38 weeks' gestation and 3 months post partum. Measurements of cardiac output, heart rate, and stroke volume were not different at 34 and 38 weeks' gestation; these results were averaged to provide a single late-gestation measurement. Although cardiac output was not affected by late gestation during this exercise protocol, the heart rate and stroke volume responses differed in late gestation compared to the postpartum period.

Table II. Rest, exercise, and recovery hemodynamics in late gestation and post partum

			Recovery			
Parameter	*Rest*	*Exercise*	*1 min*	*3 min*	*5 min*	*9 min*
Heart rate (min^{-1})						
Late gestation	79 ± 10	114 ± 17*	85 ± 16†	91 ± 16‡	89 ± 15†	88 ± 12‡
Post partum	66 ± 13	105 ± 15*	72 ± 15†	72 ± 14†	72 ± 14‡	71 ± 12
p (between groups)	<0.025	NS	<0.01	<0.001	<0.001	<0.001
Stroke volume (ml)						
Late gestation	66 ± 17	82 ± 23†	76 ± 19†	61 ± 19	63 ± 19	62 ± 17
Post partum	73 ± 22	98 ± 25*	100 ± 33*	87 ± 27‡	82 ± 26†	74 ± 20
p (between groups)	NS	<0.05	<0.005	<0.005	<0.025	NS
Cardiac output ($\text{L} \cdot \text{min}^{-1}$)						
Late gestation	5.2 ± 1.4	9.2 ± 2.7*	6.5 ± 1.7*	5.4 ± 1.5	5.3 ± 1.6	5.4 ± 1.4
Post partum	4.8 ± 0.9	10.0 ± 1.6*	6.8 ± 1.5*	6.0 ± 1.1†	5.6 ± 1.1	5.1 ± 0.9
p (between groups)	NS	NS	NS	NS	NS	NS
Systolic blood pressure						
Late gestation	113 ± 9	148 ± 20*	131 ± 18*	117 ± 10	114 ± 8	112 ± 7
Post partum	110 ± 9	134 ± 16*	125 ± 16*	112 ± 11	111 ± 11	109 ± 9
p (between groups)	NS	NS	NS	NS	NS	NS

N = 23.

*Significant within-group difference from rest value: $p < 0.001$.

†Significant within-group difference from rest value: $p < 0.05$.

‡Significant within-group difference from rest value: $p < 0.01$.

sion or heart disease and all pregnancies produced single live infants. No subject used diuretics or other cardiac medications. Ten women were prospectively identified as fit. Their characteristics were not different from those of the remainder of the study group. All subjects described a subjective decrease in exercise tolerance that was progressive during gestation. Nevertheless, the fit women continued to perform substantial exercise during gestation. Fit women exercised outside of structured classes 6.1 ± 3.2 hours per week before, 4.5 ± 2.2 hours per week during, and 5.2 ± 2.5 hours per week after pregnancy.

Hemodynamic data were obtained in 19 of 23 women at 34 weeks and in 17 of 23 women at 38 weeks of gestation. All 23 women had at least one satisfactory study in late gestation and post partum. The four incomplete studies at 34 weeks were caused by poor electrode connection in two subjects and scheduling diffi-

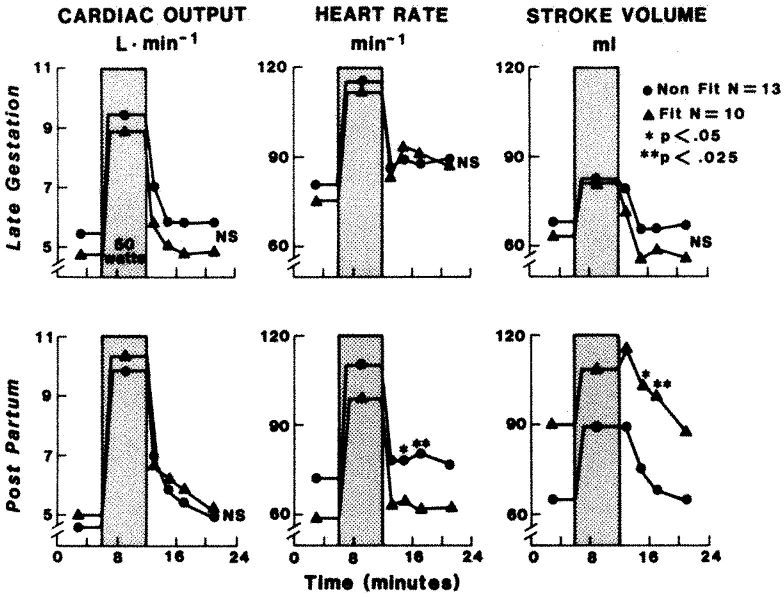

Fig. 2. Cardiac output and its components, heart rate and stroke volume, are shown at rest, during 50 W upright bicycle exercise, and during recovery in late gestation and 3 months post partum for fit and nonfit subjects. During late gestation, hemodynamics in fit and nonfit subjects were not different. Post partum, fit women had lower heart rates and larger stroke volumes at 3 and 5 minutes of recovery (analysis of variance). Less conservative statistics (unpaired *t* test) show significant differences between fit and nonfit heart rate and stroke volume at rest and exercise, in addition to recovery.

culties in the remainder. The six incomplete studies at 38 weeks were caused by poor electrode connection in one subject and earlier than anticipated delivery and scheduling difficulties in the remainder. Rest, exercise, and recovery heart rate, stroke volume, and cardiac output at 34 and 38 weeks of gestation and post partum are shown in Fig. 1. There was no difference between values obtained at 34 and 38 weeks of gestation. Accordingly, for subjects with studies at both 34 and 38 weeks, the results were averaged.

The results are detailed in Table II. Cardiac output values in subjects in the sitting position were unchanged in late gestation compared with the postpartum period at rest, during exercise, and during recovery. In contrast, heart rates were increased and stroke volumes reduced during late pregnancy. The decrement of stroke volume during late gestation was most striking immediately after exercise, when it fell to control values within 3 minutes. In contrast, stroke volume increased immediately after exercise in postpartum subjects and remained above resting values at 5 minutes of recovery. There was no difference in systolic or mean blood pressures between late gestation and the postpartum period.

The 10 prospectively identified fit women were readily recognizable as a group from postpartum studies. Heart rates were lower and stroke volumes higher than in the remainder of the subjects. However, during late gestation the heart rate, stroke volume, and cardiac output responses to exercise and recovery in the fit women were indistinguishable from those of the nonfit women (Fig. 2).

Comment

To our knowledge, this represents the first report of the response of the cardiovascular system to the onset and end of upright exercise late in human pregnancy. It should be recognized that the women volunteering for this study may not typify average North American women. They are an unusually well-motivated, health-conscious group. All had prenatal care; none smoked. We believe, nevertheless, that the conclusions from this study are not importantly altered by the bias of the subject population.

Steady-state cardiac output at rest and during exercise was not different between late gestation and the postpartum period in this study. Guzman and Caplan[9] measured cardiac output during 250 and 350 kpm · min^{-1} exercise in pregnant and postpartum subjects; they found values that averaged 2.3 L · min^{-1} higher during late gestation than during the postpartum period for 250 kpm · min^{-1} exercise and 1.2 L · min^{-1} for 350 kpm · min^{-1} exercise. This amounted to a 12% to 31% increase with the smaller difference at the heavier work load. Guzman and Caplan[9] used the indirect Fick method to determine output by measuring disappearance of an inhaled gas (nitrous oxide) and they did not report resting cardiac output. Ueland et al.[2] used an indicator dilution technique (indocyanine green) to measure cardiac output. Resting output in 11 subjects in the sitting position was 5.2 $L \cdot min^{-1}$ in late gestation and 5.0 $L \cdot min^{-1}$ post partum. These values are not different from those reported in the present study. During exercise, cardiac output was 19% higher at 100 $kpm \cdot min^{-1}$ and 5% lower at 200 $kpm \cdot min^{-1}$ during late gestation than post partum. We conclude that in late gestation steady-state cardiac output at rest in the sitting position is not different from postpartum values. Furthermore, cardiac output during upright bicycle exercise is the same or only slightly greater in late gestation compared to postpartum.

The components of cardiac output, heart rate, and stroke volume are also similar in all three studies. Ueland et al.[2] found that sitting heart rate was 8 bpm higher in late gestation than post partum; during exercise, heart rate was 14 to 17 bpm higher in late gestation than post partum. In Guzman and Caplan's[9] study, heart rate was approximately 12 bpm higher during exercise in late gestation than postpartum. Stroke volume was the same at rest in late gestation and post partum in the study by Ueland et al.,[2] and during exercise, stroke volume in late gestation was not different from the postpartum value. In Guzman and Caplan's[9] study, stroke volume in late gestation averaged 12% above the postpartum value during exercise. In our study, stroke volume was reduced 14% at rest and 17% during exercise in late gestation compared with postpartum values; only the difference during exercise reached significance. We conclude that, in late gestation, heart rate in the sitting position is increased both at rest and during exercise, whereas stroke volume does not appear to be importantly different between late gestation and the postpartum period except during recovery.

Since stroke volume normally increases early during graded exercise,[10] we interpret these findings to mean that the available resources for increasing stroke volume during late pregnancy are fully used. This is further supported by the higher heart rates. We can only conclude that in late gestation upright exercise stroke volume is not affected by the increased heart size[5] and blood volume[4] reported by others. The hypothesis that venous return in the upright position is responsible for this discrepancy is supported by the observations at the end of exercise. Stroke volume during late gestation drops precipitately during recovery in contradistinction to the rise in stroke volume seen in postpartum subjects and in other reported studies[11] after exercise. The active muscle pump of the working legs may be necessary to force blood past the uterus or to overcome hydrostatic pressure in an overly compliant venous bed.

Considering the similarity of the steady-state measurements of output in this study by impedance cardiography to those from two studies[2, 9] in which modified Fick techniques were used, we are confident about the reliability of impedance cardiography during pregnancy. Our initial evaluation of this technique revealed a satisfactory, though less precise, measurement of output in patients undergoing cardiac catheterization. Others have used this technique to assess output at rest, during exercise,[7, 12] and in response to various stresses[13, 14] and have reported good correlations with indicator dilution techniques. There is one report that the technique failed to assess stroke volume accurately.[15] Studies made by others during pregnancy,[16] although not substantiated by independent output measurements, show results similar to those of Ueland et al.[2] regarding the effects of posture and the duration of gestation on stroke volume. Secher et al.[17] measured cardiac output by impedance and by thermodilution in women undergoing elective cesarean section and concluded that "the impedance method is reliable for measuring cardiac stroke volume in late pregnancy under physiologic conditions in the conscious patient." We believe that our experience and that of others support the view that impedance cardiography gives accurate data about individual changes in stroke volume and that accurate group averages are obtainable with this technique.

We were surprised that fit women were indistinguishable from the remainder of the study group during late gestation. Normally, fit subjects respond to exercise with a greater stroke volume and a slower heart rate at a fixed work load than do nonfit subjects, and we found this expected result post partum. We incorrectly hypothesized that prior aerobic training would improve hemodynamics throughout gestation. There are similarities between the cardiac changes characteristic of pregnancy[5] and those associated with chronic isotonic training.[18] In both situations, the heart is enlarged, with normal systolic function. However, the athlete's heart enlarges proportionally; the wall increases in thickness to the same extent as the enlargement of ventricular diameter; during pregnancy, wall thickness remains nearly constant. There are several possible explanations for the absence of a training effect in late gestation. It is possible that advanced pregnancy causes activity limitations in fit women that allow detraining to occur. Saltin et al.[19] have shown the rapid regression of training effects with 3 weeks of bed rest. Trained levels were regained 20 to 40 days after the reinstitution of exercise. This could explain why the fit women were different from the controls during the postpartum study. We doubt that detraining was a major factor in this study. The majority of the fit women continued substantial exercise activities to the end of pregnancy. Alternatively, the unfit women may have been "trained" by the fitness class during pregnancy. Collings et al.[20] have demonstrated increased aerobic capacity in response to an exercise program during pregnancy. Their program was substantially more rigorous than our Fitness in Pregnancy class. Exercise training was performed on the bicycle ergometer for 25 minutes three times weekly at an average heart rate of 152 bpm. Since exercise stroke volume in our nonfit group was lower in late gestation than postpartum, we doubt that cardiovascular training in the exercise class caused the responses of the fit and nonfit groups to merge in late gestation.

The best explanation that we can suggest for the lack of training effect during late gestation is inadequate venous return. As Krogh[21] recognized, "The heart cannot do more than send out what it gets." Implicit in this hypothesis is the concept that blood volume, posture, and venous capacitance are the dominant hemodynamic determinants during late gestation. Despite a vastly expanded blood volume, late gestation is not characterized by plethora and an increased stroke volume. Rather, in many situations the heart receives a marginal venous return.

If cardiac output is marginal or inadequate, a choice must be made between maternal and fetal tissue. Laboratory investigation in animals suggests that, during exercise, uterine blood supply falls but placental flow may be preserved.[22] The relevance of these data to humans is conjectural because we, uniquely, jeopardize venous return by maintaining the upright position. Epidemiologic data show lower birth weights in humans when mothers continue upright work during pregnancy.[23]

The rapid fall in stroke volume at the end of exercise in late gestation deserves further comment. Normally, stroke volume increases because of augmented end diastolic dimension and increased systolic shortening,[11] the latter attributed to sustained elevation of contractility due to circulating catecholamines coupled with a lower arterial pressure at the end of exercise. This suggests that in late gestation end-diastolic volume during recovery from exercise may be even smaller than it was during the initial resting period. Possibly, factors other than the upright posture or vena caval obstruction are at work. During exercise, increased blood flow to working muscles and skin (for heat loss) tends to increase venous capacitance. This is offset normally by adrenergic vasoconstriction in other capillary beds.[24] Perhaps adrenergic regulation of arterial tone and venous capacitance is altered in pregnancy, to the detriment of venous return during exercise. Reduced vasomotor function in pregnancy has been suggested.[25] Alternatively, veins draining working muscles or thermoregulatory beds may be enlarged; vasodilation could result in an increased venous capacitance that would overwhelm compensatory vasoconstriction in other beds.

Facilities for the Fitness in Pregnancy class are generously provided by the Portland Metro YMCA.

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Implantation site in complete molar pregnancy: A study of immunologically competent cells with monoclonal antibodies

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The nature and intensity of inflammatory cellular infiltrate in the implantation sites of 10 complete molar pregnancies were evaluated by immunohistochemical staining of frozen tissue sections with monoclonal antibodies. As compared to the implantation site in normal pregnancy, there was an increase in the number of infiltrating inflammatory cells in the molar implantation site. Most of the inflammatory cells were T cells with predominance of T4$^+$ (Leu-3a$^+$) cells over T8$^+$ cells. Inflammatory cells were not detected in the molar vesicles. The possible implications of these findings in molar pregnancy are discussed. (AM J OBSTET GYNECOL 1985;152:97-9.)

Key words: Complete hydatidiform mole, cellular immune response

Gestational trophoblastic neoplasms are of special interest because of their unique biologic property of arising in the conceptus and invading the pregnant woman and because of their favorable response to chemotherapy. Recent studies demonstrated that most complete hydatidiform moles have chromosomes entirely of paternal origin. Thus they can be considered as complete allografts in a (presumably) immunologically competent host. To examine whether this allograft status initiates an immune response that may account for their favorable prognosis, we previously reported the lack of deposition of immunoglobulin and complement at the molar implantation site. In the current study monoclonal antibodies that react with immunologically competent cells were used to determine the nature of cellular immune response in the moles and their implantation sites.

Material and methods

Tissue samples were obtained from three evacuated moles and from sharp curettings of 10 molar implantation sites and were frozen in OCT compound. Then 4 μm cryostat sections were fixed in acetone and stained with monoclonal antibodies by an avidin-biotin immunoperoxidase technique (Vector Laboratories). The monoclonal antibodies used are commercially available from Becton-Dickinson (the Leu series), Ortho Diagnostics (the OK series), Coulter Immunology [Coulter clones (cc) series] and Hybritech, [Anti-common leukocyte antigen, (T200)]. These antibodies react as follows: anti–Leu-4 is a pan–T cell reagent; anti–Leu-3a and anti-T4 (cc) react with helper/inducer T cells (class II MHC antigens reactive cells) and macrophages; OKT8 reacts with cytotoxic/suppressor T cells (class I MHC antigens reactive cells); anti-B1 (cc) reacts with all B cells except plasma cells; OKM1 reacts with gran-

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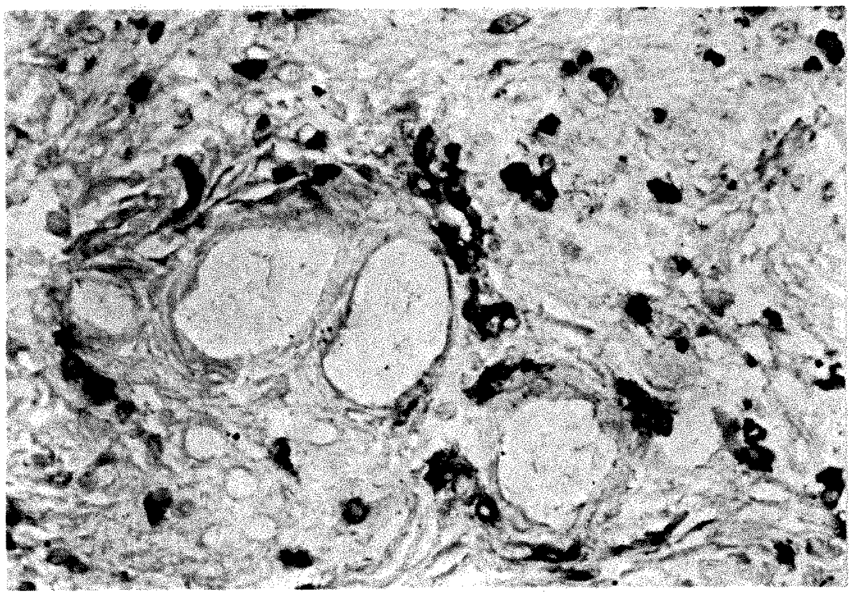

Fig. 1. Cryostat section of the implantation site of a molar pregnancy stained with anti–Leu-3A antibody. Many Leu-3a$^+$ cells are present in the perivascular location. (Immunoperoxidase with hematoxylin counterstain, ×400).

ulocytes, macrophages, and natural killer cells; anti–Leu-7 reacts with natural killer cells. Negative control sections from each case were also stained with OKT6 antibody, which reacts with thymocytes and Langerhans/indeterminate cells or with the second developing antibody alone. One section from each case was also stained with anti–HLA-DR (Ia-like) (Becton-Dickinson). The infiltrating inflammatory cells were counted in 10 random consecutive high-power microscopic fields, and the average was calculated.

Results

There was no staining with anti-T200 antibody in the molar vesicles, indicating the absence of infiltrating inflammatory cells and of Hofbauer cells.[1] Molar vesicles were HLA-DR negative.

In contrast, in the molar implantation site there was a moderate increase in infiltrating inflammatory cells as compared to normal pregnancy.[1] The majority of infiltrating cells were T lymphocytes (Leu-4$^+$), averaging about 15 cells per high power field (range 3 to 47) as opposed to 3 to 4 T cells per high power field in normal pregnancy.[1] In all cases the number of T4$^+$, Leu-3a$^+$ cells was larger than that of Leu-4$^+$ cells. This is due to the presence of numerous T4$^+$, Leu-3a$^+$ macrophages in the decidua as previously reported.[1] However, when the number of T8$^+$ cells was compared with that of total T cells (Leu-4$^+$ cells), T8$^+$ cells were still in the minority, contributing about one quarter to one third of the total number of T cells. Thus most of the increased T cells at the molar implantation site are T4$^+$. In 6 of 10 molar implantation sites, these T4$^+$, Leu-3a$^+$ cells were located primarily around blood vessels (Fig. 1). Many of the tissue macrophages stained with anti–HLA-DR antibody and some with OKM1.

Polymorphonuclear leukocytes stained intensely with OKM1 antibody and were found diffusely infiltrating the decidua. Leu-7$^+$ cells and B1$^+$ lymphocytes were extremely rare.

Comments

Our findings indicate that there is an average fourfold increase in T cell lymphocytic infiltrate in the molar implantation site as compared to the implantation site of normal pregnancy. Although of markedly less intensity, the lymphocytic infiltrate in the molar implantation site is reminiscent of cellular infiltrates observed in skin allograft bed and delayed hypersensitivity reactions in skin, especially in the abundance of T4$^+$ (Leu-3A$^+$) cells and their presence in perivascular location. In skin allografts undergoing rejection,[2] a marked T cell infiltrate is present, with T4$^+$ cells more abundant in the dermis, especially perivascularly, while T8$^+$ cells infiltrate the epidermis. In contrast, no inflammatory infiltrate is noted here in the molar chorionic villi. This may suggest a lack of recognition by the maternal immune system of the villous trophoblast which does not express major histocompatibility antigens. As the T cell infiltrate was restricted to implantation site (maternal tissues), it is unlikely that T cells were initiating a direct cytotoxic reaction. Therefore it is possible that T4$^+$ (Leu-3A$^+$) cells may be inducing a delayed hypersensitivity type of reaction in the molar implantation site, leading to vascular changes with resulting ischemia and subsequent abortion or rejection of the molar pregnancy.

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Interferon responses in maternal and fetal mice

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The kinetics of maternal-fetal interferon and a chemical interferon inducer were studied in Swiss-Webster white mice at 8, 15, and 19 days of gestation. Crude interferon was administered by maternal tail vein injection to one group. There was no transfer of interferon to the fetus despite high maternal levels. A chemical interferon inducer (10-carboxymethyl-9-acridanone) was given intramuscularly to a second group. Both maternal and fetal interferon responses rapidly reached significant levels, although the fetal response was less than that of the mother. Presence of the inducer was demonstrated in both maternal and fetal samples, indicating placental transport of the chemical to the fetus. The implications of these findings for the fetal immune response are discussed. (AM J OBSTET GYNECOL 1985;152:99-102.)

Key words: Interferon, mice, placental transfer

Interferon is a protein with well-recognized antiviral activities. It occurs as one of the most immediate immune responses, appearing within hours of the presence of viral double-stranded RNA in the cytoplasm.[1] There are also chemical inducers capable of stimulating interferon synthesis or release. Interferon accomplishes a number of complex actions at the cellular level, but it clearly plays a key role in modulating the response to infectious challenge, particularly from viruses.

The mature fetus and neonate possess interferon response capabilities.[2] Indirect evidence through animal and human cell culture studies exists for the presence of interferon production earlier in fetal life.[3-7] The exact function of interferon in the developing fetus is not clear. Yet the role of interferon in extrauterine life indicates that it may assume equally important functions in the fetus. Little is known about its dynamics between mother and fetus or the fetal interferon response to a chemical interferon inducer.

This study was designed to directly investigate the kinetics of maternal-fetal interferon during pregnancy in an animal model. The first objective was to determine both maternal and fetal responsiveness to nonviral interferon stimulation at various stages of gestation. We also evaluated the placental capacity for transfer of interferon and an interferon inducer.

Material and methods

Mice. The mouse was selected for study on the basis of cost, ease of handling, and availability of a supply of species-specific interferon and of the chemical inducer 10-carboxymethyl-9-acridanone. Swiss-Webster white mice with a total gestational life of 19 to 20 days were used with timed pregnancies. Mice were obtained as insemination-dated groups from Charles River Laboratories in Wilmington, Massachusetts. Shipment arrivals were coordinated to correspond to investigation at 8, 15, and 19 days' gestation. Fetal implantation takes place on day 4 or 5 so that prior to day 8 of gestation, the uterus and fetus were too small to allow reliable recovery of fetuses for analysis.

Interferon. Commercially available interferon was initially used and found to be of insufficient quality to give detectable levels. Therefore crude murine interferon was prepared by inducing mouse L cells with Newcastle disease virus. After the cells had grown to confluence, 100 EID_{50} of virus per cell was added and incubation was carried out overnight. The following day the supernatants were harvested and analyzed against pH 7 citric acid for 5 days and phosphate-buffered saline solution for 24 hours. Supernatants were then centrifuged at 25,000 rpm for 90 minutes in a

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Table I. Interferon titers after maternal tail vein inoculation with crude interferon

	0 min (IU)	*10 min (IU)*	*30 min (IU)*	*60 min (IU)*	*120 min (IU)*
8 days' gestation					
M. S.	0	80	80	40	20
A. F.	–	–	–	–	–
F. H.	0	0	10	0	0
15 days' gestation					
M. S.	0	160	80	40	0
A. F.	0	0	0	0	0
F. H.	0	0	0	0	0
19 days' gestation					
M. S.	0	80	40	20	–
A. F.	–	–	–	–	–
F. H.	0	0	0	0	–

Table II. Interferon induction by 10-carboxymeth-9-acridanone

	0 hr (IU)	*1 hr (IU)*	*2 hr (IU)*	*4 hr (IU)*	*8 hr (IU)*
8 days' gestation					
M. S.	0	2560	5120	2560	640
A. F.	–	–	–	–	–
F. H.	0	0	320	320	1280
15 days' gestation					
M. S.	0	2560	2560	2560	160
A. F.	0	0	40	160	20
F. H.	0	10	320	160	20
19 days' gestation					
M. S.	0	1280	1280	1280	640
A. F.	0	–	–	–	–
F. H.	0	0	10	320	604

Spinco L-2B Ultracentrifuge. The interferon-containing solutions were then frozen at −80° C until use.

Interferon assays. Interferon assays were performed by means of a microtiter system that utilizes murine L cells and vesicular stomatitis virus. The assay is read by cytopathic inhibition. The last dilution inhibiting 50% of the cytopathic effect compared to the control is termed the interferon titer. All assays incorporated an internal interferon standard titered against National Institutes of Health reference No. G006-904-511. The latter in our system titers 800 U. Titers are expressed in international units. The minimum sensitivity of interferon detection in this system is 10 IU.

Murine experiment. Two separate groups of mice were studied. Study of each group was repeated twice, and interferon samples were frozen and independently double checked. Group 1 was directly injected via tail vein with 7500 U of crude mouse interferon in a 0.6 cc volume. Control mice not receiving interferon were sacrificed at time O. Subsequently, groups of three to five injected mice were put to death at 10, 30, 60, and 120 minutes after interferon injection. Maternal serum and as many fetuses as possible were collected and pooled from each batch of mice. Pooled fetuses were homogenized with 0.5 ml of phosphate-buffered saline solution and then clarified by centrifugation as the fetal homogenate. The supernatant was designated as the fetal homogenate. Amniotic fluid was obtainable only in pregnancies of 15 days' gestation, the quantity being insufficient for collection at 8 and 19 days.

Group 2 underwent interferon induction by intramuscular injection of 30 mg of 10-carboxymethyl-9-acridanone. This is a highly soluble compound that is a potent species-specific inducer of interferon in the mouse and hamster.[8] Adult and newborn mice have a 10-carboxymethyl-9-acridanone interferon response that is particularly rapid and intense within 1 to 2 hours after injection. Batches of three to five mice were put to death and specimens collected as in the first group, but at intervals of 1, 2, 4, and 8 hours. Control mice, not receiving 10-carboxymethyl-9-acridanone, were tested similarly to the experimental mice. A longer period of observation was selected for the inducer-treated mice compared to that of the interferon-treated mice because of the longer period of detectable interferon levels.

Levels of 10-carboxymethyl-9-acridanone in each pooled specimen were analyzed by spectrophotofluorometry. A Specs-fluo-log measured relative fluorescence at 440 μm after excitation at 250 μm.[9]

Results

Group 1. The maternal and fetal response to direct maternal tail vein injection of interferon is detailed in Table I. As expected, maternal interferon titers rose quickly following injection at all gestational ages, peaking rapidly in 10 to 30 minutes. There was no evidence of interferon activity in any of the fetal or amniotic fluid samples, indicating that the exogenous maternal interferon did not cross the placenta to the fetus. Control samples did not demonstrate the presence of any interferon-like activity.

Group 2. Interferon response and 10-carboxymethyl-9-acridanone levels are presented in Tables II and III, respectively. Administration of 10-carboxymethyl-9-acridanone induced the presence of interferon in all maternal and fetal samples including amniotic fluid. Maternal levels appeared within 1 hour and peaked by 2 hours. Interferon presence in the fetal homogenate lagged slightly behind the maternal levels while amniotic fluid values were delayed even further. The time lag sequence is consistent with the concept of gradual equilibration of 10-carboxymethyl-9-acridanone across the placenta to the fetus and amniotic fluid. Determination of 10-carboxymethyl-9-acridanone levels con-

Table III. Levels of 10-carboxymeth-9-acridanone

	Control (mg/ml)	*1 hr (mg/ml)*	*2 hr (mg/ml)*	*4 hr (mg/ml)*	*8 hr (mg/ml)*
8 days' gestation					
M. S.	0	827	184.6	92.8	151.2
A. F.	–	–	–	–	–
F. H.	0	382.3	35.6	7.4	31.4
15 days' gestation					
M. S.	0	751.9	646.7	24.3	0
A. F.	0	126.2	214.6	138.7	24.0
F. H.	0	174.5	265.5	153.7	23.3
19 days' gestation					
M. S.	0	827	827	74.5	11.3
A. F.	–	–	–	–	–
F. H.	0	137	129.5	108.7	44.2

firmed that the chemical was present in all these fluids at all gestational ages but at lower levels in fetal samples compared to maternal samples.

Comment

Concepts of protection of the fetus from the threat of viral infection have traditionally concentrated on the dynamics of humoral immunity, particularly in the form of antibodies. The fetal antibody response is limited and ineffective early in pregnancy and certainly not capable by itself of routinely deterring fetal viral infection. Maternally acquired antibodies are more effective but not present in large number until late in pregnancy. The cellular and nonimmunoglobulin secretory components of the fetal immune response have received little attention. However, by 10 weeks' gestation, T cells are present in the peripheral fetal circulation with recognizable subtypes at 14 weeks.[10] These findings suggest that, just as in infancy and adulthood, there is more to the fetal immune response than active and passive antibodies. Interferon could be a potential weapon against fetal viral infection, especially since the interferon response can be rapidly mobilized and is active against a wide range of viruses.

Specific information on the human fetal interferon response does not exist. Desmyter et al.[11] were unable to detect circulating interferon in infants with congenital rubella; however, they demonstrated that these children possessed an appropriate interferon and antibody response to measles vaccination. Several authors have evaluated human fetal and neonatal leukocyte interferon response in cell culture at varying gestational ages. Emodi and Just[12] found that leukocytes from infants with congenital cytomegalovirus responded to stimulation with only small amounts of interferon whereas asymptomatically shedding infants have the same interferon response as virus-free infants. Ray,[2] Carter et al.[7] and Banatvola et al.[5] all concurred that human fetal cells at 10 to 24 weeks' gestational age when stimulated by virus challenge in vitro possessed an interferon response at least equal to infants and adults. Subsequently, Bryson et al.[13] demonstrated that cells from neonates had decreased capacity to produce γ-interferon, but produced α-interferon in normal quantities.

Three groups have studied interferon responsiveness of intact fetal animals. All three demonstrated fetal interferon production after virus challenge in the second and third trimesters.[3, 4, 6] Only Overall found interferon in the first trimester using fetal lambs but at very low levels. Subsequently, he was unable to demonstrate placental transfer of interferon late in sheep pregnancies. Both Overall and Barbosa found strong maternal interferon responses to viral stimulation.

In our system it is not possible to be certain that the interferon found in the fetus is strictly fetal and not of maternal origin. Since our data and that of others suggest interferon does not readily cross the placenta, it seems likely that we are measuring interferon of fetal origin. The levels of interferon found circulating after 10-carboxymethyl-9-acridanone injection were considerably higher than after interferon injection and were maintained for a longer period. It is possible that such high levels could have permitted transplacental interferon passage.

Regardless of interferon's origin, it is clear that there is an intact response in gravid animals from the second trimester through term. Quantitatively, the responses were similar regardless of gestational age. They corresponded with the responses in nonpregnant adult mice in Taylor's study. This is the first demonstration that high levels of fetal interferon can be found in the fetus after induction by an exogenously administered chemical compound (10-carboxymethyl-9-acridanone) instead of a virus. Further, the levels of interferon in the fetus during induction were substantial. Placental permeability to the chemical inducer was confirmed by direct assay.

If the interferon found in the fetus is of fetal origin as we suspect, then we may assume that the fetal interferon response is present relatively early in intrauterine life, perhaps as early as the late first trimester. It occurs at a time when virtually all known components of the immune system are nonexistent or immature. However, the exact functional maturity of fetal interferon remains open to question. Neonatal interferon subtype production is known to be incomplete.[13] α-interferon and β-interferon response is equivalent to that of adults, while γ-interferon is deficient. The latter has a greater cell growth inhibitory effect than other interferons.

Many questions remain to be answered about fetal interferon and its potential applications. Its cell growth inhibitory effect could be responsible for the congenital anomalies or intrauterine growth retardation that is frequently associated with fetal viral infection. It is not known for what length of time the fetus produces interferon when undergoing viral challenge, nor is it clear whether interferon alone can protect the fetus. The function of natural and exogenous chemical interferon inducers in stimulating the system also requires investigation. Clearly, the fetal immunologic response is more complex than we have appreciated. A more complete understanding of the system may allow us to utilize it to improve fetal and neonatal survival.

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Eutopic and ectopic macromolecular human placental lactogen

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Macromolecular forms of human placental lactogen have received little attention because it has been thought that such forms either compose only a small fraction of total immunoactive placental lactogen or are merely laboratory artifacts. We examined serum and placental tissue from women with normal pregnancy (first and third trimesters), serum and tissue from women with eutopic tumors (mole and choriocarcinoma), and serum from men with ectopic placental lactogen production. Samples were chromatographed on dextran gel (Sephadex G-100), and placental lactogen was measured in the fractions by radioimmunoassay. In all specimens examined, immunoactive placental lactogen was found at the void volume of the column (molecular weight >150,000 daltons). This macromolecular placental lactogen comprised <4% of total placental lactogen in the third trimester, in mole, and in 16 of 18 first-trimester samples but was significantly higher, up to 19%, in the malignant cases. In two first-trimester placental extracts (but not in their matched sera) macromolecular placental lactogen was the dominant (>45% of the total placental lactogen) immunoactive species. Authentic monomeric placental lactogen was not converted to macromolecular placental lactogen by repeated freezing and thawing. Third-trimester placental macromolecular placental lactogen was unstable; only 13% remained at the void on rechromatography. First-trimester placental macromolecular placental lactogen, on the other hand, was stable to rechromatography. The behavior of immunochemical dilutions of macromolecular placental lactogen from first-trimester placenta was similar to that of monomeric placental lactogen in the same sample. Macromolecular placental lactogen is probably not artifact, and it can comprise a large fraction of the total immunoactive placental lactogen in certain conditions. (AM J OBSTET GYNECOL 1985;152:103-11.)

Key words: Human placental lactogen, macromolecular, gel chromatography, radioimmunoassay

The lactogens or mammotropins, including prolactin, placental lactogen, and growth hormone, are a family of proteins with similar molecular weights, similar immunologic and biologic properties, and extensive homology in the structure of their genes. They probably derive from a common ancestral gene.[1] Size heterogeneity, including both dimeric and macromolecular forms, has been extensively documented for growth hormone[2, 3] and for prolactin.[4] However, with the notable exception of a well-characterized interchain disulfide dimer of placental lactogen,[5] the macromolecular forms of placental lactogen recognized ever since the early in vitro studies of Suwa and Friesen[6] have received much less attention. Part of this neglect has related to the belief that such macromolecular forms, if present at all in vivo, comprise only a very small fraction of total immunoactive placental lactogen or are merely laboratory artifacts.

In this study, we have looked for macromolecular placental lactogen in serum and placental tissue from women at term and in the first trimester of pregnancy, in serum and tissue from women with eutopic benign and malignant tumors of the placenta, and in serum from men with ectopic placental lactogen production.

Methods

Sera and tissues. Term maternal peripheral venous blood and term placentas were obtained at vaginal delivery, kept on ice, and processed within 30 minutes. The clotted blood was centrifuged at 1,000 × g for 15 minutes; the serum was separated, centrifuged at 100,000 × g for 1 hour, and chromatographed immediately. Placental tissue was freed of membranes and fibrous tissue, and was washed with cold saline solution until visibly free of blood. Ten grams was homogenized in a Waring Blendor at high speed for 1 minute in 100 ml of an ice-cold solution of phosphate-buffered saline (0.01 mol/L of sodium phosphate, pH 7.4, 0.15 mol/L of sodium chloride, and 0.0003 mol/L of sodium azide [PBSA]) containing the protease inhibitors aprotinin and phenylmethylsulfonyl fluoride (PBSAI). The resulting tissue extract was centrifuged at 1,000 × g for 20 minutes; the supernatant was separated, centrifuged at 100,000 × g for 1 hour, and the final clear supernatant was chromatographed immediately.

Peripheral venous blood was obtained from the patients with hydatidiform mole on the day before

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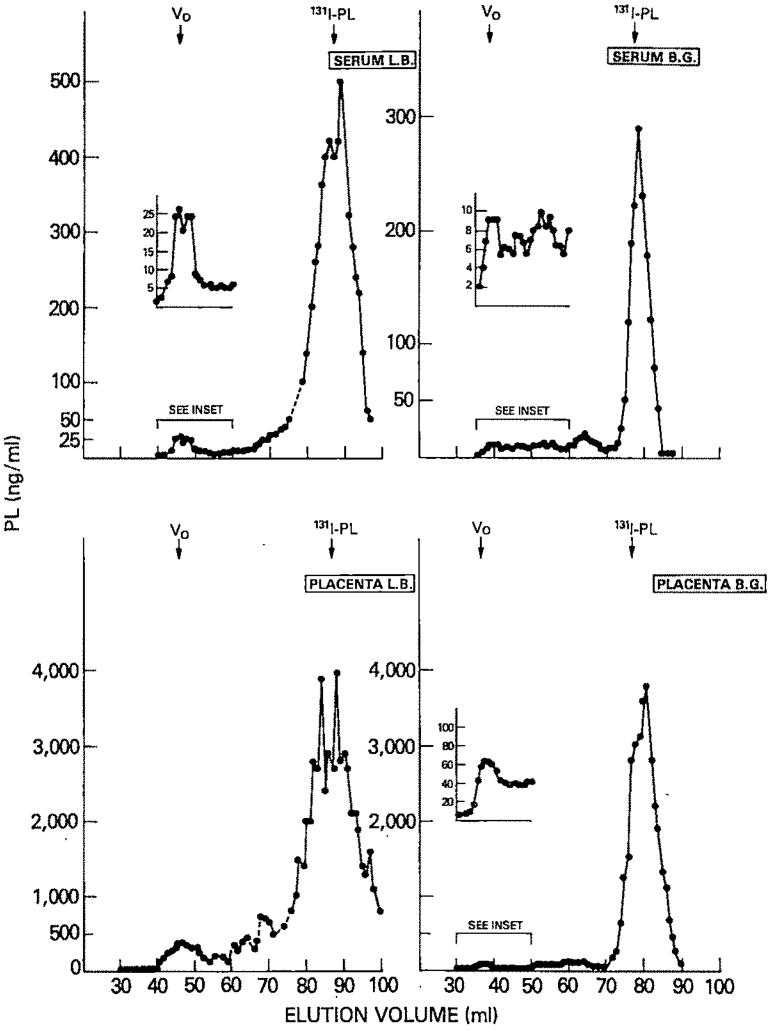

Fig. 1. Gel chromatography on Sephadex G-100 of sera and placental extracts from two women (L. B. and B. G.) at term. V_o denotes the void volume and *^{131}I-PL* denotes the elution volume of cochromatographed radioiodinated monomeric placental lactogen. *Dashed lines* represent fractions not assayed because of technical problems.

evacuation and was centrifuged at 1,000 × g for 15 minutes. The serum was separated and frozen for 1 week to 2 months. The serum was then centrifuged at 100,000 × g for 1 hour and stored at 4° C for 1 to 5 days until chromatographed. Tissue from these patients was washed immediately with cold saline solution until visibly free of blood and frozen for 1 week to 2 months. Samples of 2.0 and 3.6 gm were homogenized in glass (tissue grinder, Ten Broeck, Corning) in 10 ml of PBSAI, and the extract was processed as described above. The extract was stored at 4° C for 1 to 5 days until chromatographed.

Serum from two men with ectopic placental lactogen–producing tumors and serum from a woman with gestational choriocarcinoma (provided by Dr. Leo Twiggs) had been frozen at −20° C for several years. The thawed sera were centrifuged at 100,000 × g for 1 hour, just prior to chromatography.

Peripheral venous blood from women in the first trimester of pregnancy was obtained 1 to 2 hours before abortion. The blood was kept on ice for 4 hours and centrifuged at 1,000 × g for 15 minutes. The serum was separated and stored overnight at 4° C. It was then centrifuged at 100,000 × g for 1 hour and stored at 4° C for 2 to 3 weeks until chromatographed. Placental tissue from these women was kept on ice for 4 hours, washed with cold saline solution until visibly free of blood, and stored at 4° C overnight. Five grams was then homogenized in glass in 5 ml of PBSAI and processed as described above. The extract was stored at 4° C for 2 to 3 weeks until chromatographed. All centrifugations were carried out at 4° C.

Gel chromatography. Supernatant in amounts of 1 or 2 ml of either serum, placental extract, or tissue extract was applied to a 1.5 by 90 cm column of beaded dextran gel (Sephadex G-100) that had previously been

Table I. Heterogeneous forms of eutopic and ectopic placental lactogen: percent recovered by G-100 chromatography

		Serum			*Tissue*		
Patient	*Diagnosis*	*Void*	*Dimeric*	*Monomeric*	*Void*	*Dimeric*	*Monomeric*
L. B.	Pregnancy, third trimester	2.6	?	88	6.0	7.7	87
F. P.	Pregnancy, third trimester	2.7	2.4	89	0.2	?	94
D. O.	Pregnancy, third trimester	1.2	3.0	91			
B. G.	Pregnancy, third trimester	3.4	6.0	85	0.6	2.0	90
L. C.	Pregnancy, third trimester	2.0	2.6	94			
R. A.	Pregnancy, third trimester	2.3	2.1	95			
No. 1	Pregnancy, first trimester	2.5	0.7	95	46	9.2	27
No. 2	Pregnancy, first trimester	0.3	0.6	97	44	11	37
Pool of 13	Pregnancy, first trimester				3.0	<0.6	97
No. 3	Pregnancy, first trimester				3.3	0.9	93
No. 4	Pregnancy, first trimester				0.7	0.2	99
No. 5	Pregnancy, first trimester				<0.3	0.3	99
S. M.	Hydatidiform mole	4.3	?	88	0.9	1.8	97
D. P.	Hydatidiform mole	1.8	?	92	0.9	1.8	95
P. S.	Choriocarcinoma	9.2	ND	90			
M. M.	Stomach carcinoma	11	ND	88			
G. C.	Retroperitoneal carcinoma	19	ND	81			

? = Shoulder on monomer peak; ND = not detected.

calibrated with purified, nonglycosylated, globular proteins of known molecular weight; the column was eluted with PBSA containing 0.01% (w/v) ovalbumin at a flow rate of 5 to 7 ml/hr. In some experiments, third-trimester serum and term placental extract were also applied to a 1.5 by 90 cm column of polyacrylamide gel (Bio Gel P-150). Trace quantities of iodine 125–labeled porcine thyroglobulin (to mark the void volume), ^{125}I or iodine 131–labeled placental lactogen, and ^{125}I-labeled sodium iodide (to mark the salt peak) were cochromatographed in each run as internal markers. In some experiments, ^{125}I-labeled ovalbumin (molecular weight 45,000), to mark the elution volume of the placental lactogen dimer,[5] was also cochromatographed. All gel chromatography was carried out at 4° C except for a single serum that was chromatographed at room temperature. Fractions of 1 ml were collected and stored at 4° C until assayed. Estimation of the elution volume and quantitation of asymmetric peaks were done by triangulation.

Radioimmunoassay. All fractions were analyzed for placental lactogen by a double-antibody radioimmunoassay according to our previously published method,[7] with minor modifications. Two types of assay were used: a 37° C overnight rapid assay and a more sensitive 6-day assay at 4° C, with delayed addition of labeled placental lactogen. Immunoassayable placental lactogen in tissue extracts was not affected by the homogenization technique (data not shown). Immunochemical dilutions were performed in solutions containing protease inhibitors[8]: phenylmethylsulfonyl fluoride (1 mmol/L), aprotinin (1,000 U/ml), and soy bean trypsin inhibitor (0.1%). Testing for parallelism was done according to Rodbard.[9]

Results

Third-trimester sera and term placentas. Six third-trimester sera were chromatographed on Sephadex G-100. Typical elution profiles are shown in the *upper panels* of Fig. 1. Three species of immunoactive placental lactogen were almost invariably found. The dominant species coeluted with labeled monomeric placental lactogen and comprised 85% to 95% of the total placental lactogen recovered (Table I). A second species eluting in the region of dimeric placental lactogen[5] comprised 2.1% to 6.0%. A third species (Fig. 1, *inset* to *upper left panel*), comprising 1.2% to 3.4% of the total placental lactogen recovered, eluted at the void volume of the column. Occasionally (Fig. 1, *inset* to *upper right panel*) an additional peak of immunoactive placental lactogen was seen eluting near but not at the void volume. Calibration of the column in a separate experiment gave apparent molecular weights of 25,000 for monomeric placental lactogen, 47,000 for dimeric placental lactogen, and >150,000 for void volume placental lactogen.

Elution patterns were unchanged whether serum was chromatographed at room temperature or at 4° C, but the total recovery of applied placental lactogen at 4° C averaged 85% while the recovery at room temperature was much less (data not shown). There was no difference in the elution patterns of serum chromatographed on polyacrylamide (Bio-Gel P-150) (data not shown). Neither freezing and thawing (15 times) nor dialysis against PBSA altered the amount or elution position of immunoactive void volume placental lactogen from unfractionated third-trimester serum.

Extracts of three normal term placentas were chromatographed on Sephadex G-100. Typical elution pro-

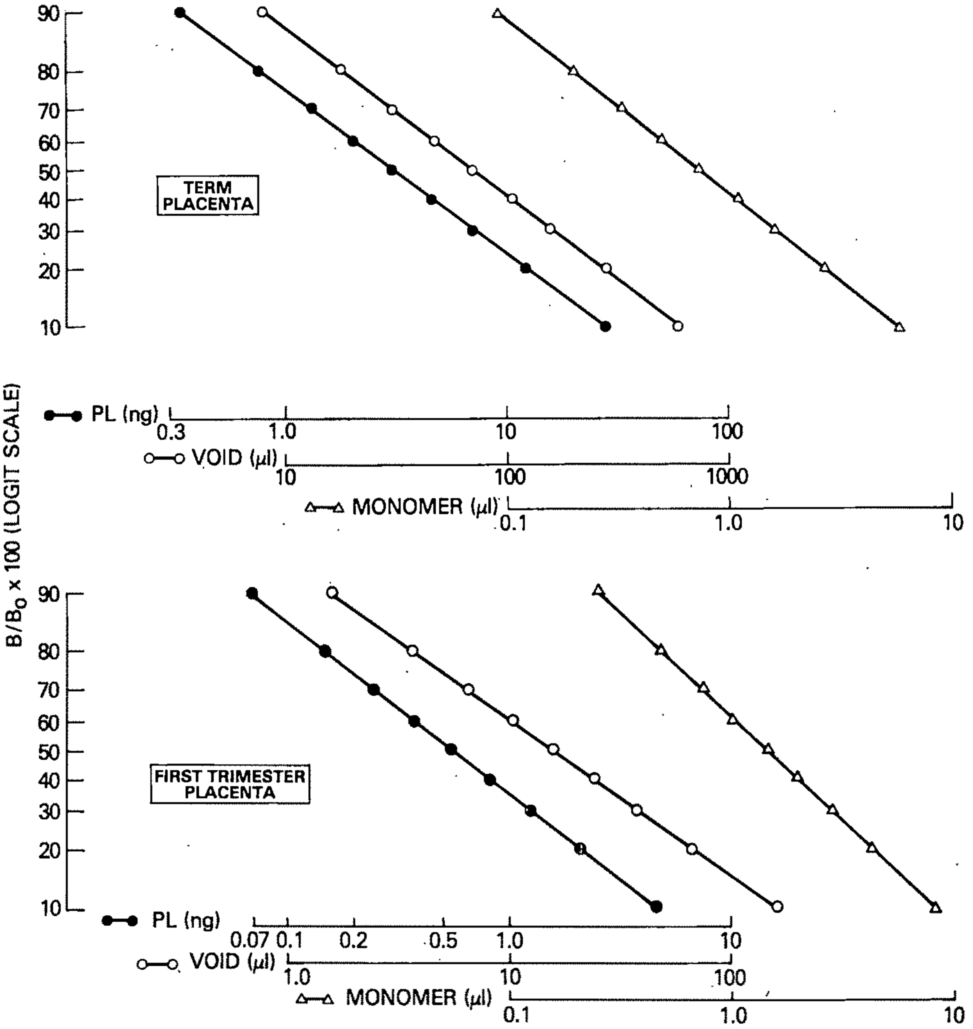

Fig. 2. Immunochemical dilutions of purified standard placental lactogen from placenta and immunoactive forms of placental lactogen in extracts of term and first-trimester placentas. *Upper panel:* Serial dilutions of purified standard placental lactogen and void volume and monomeric placental lactogen from a term placental extract chromatographed on Sephadex G-100. *Lower panel:* Serial dilutions of purified standard placental lactogen and void volume and monomeric placental lactogen from first-trimester placental extract No. 3 (*upper right panel* of Fig. 6) chromatographed on Sephadex G-100.

files of two of these, from the same women whose serum profiles are discussed above, are shown in the *lower panels* of Fig. 1. Again, three species of immunoactive placental lactogen were found. The dominant species comprised 87% to 94% of the total placental lactogen recovered (Table I) and coeluted with marker monomeric placental lactogen. The second species comprised 2.0% to 7.7% of the total recovered placental lactogen and eluted in the region of dimeric placental lactogen. The third species comprised 0.6% to 6.0% of total recovered placental lactogen and eluted at the void volume. Immunochemical dilutions of placental lactogen from the void volume and from the monomeric regions of one of these extracts were both parallel to standard monomeric placental lactogen purified from placenta (Fig. 2. *upper panel*). When void volume placental lactogen from one of these extracts was rechromatographed, 67% migrated in the region of monomeric placental lactogen and only 13% remained at the void (Fig. 3, *upper panel*).

Serum and tissue from women with hydatidiform mole. Elution profiles of sera from two women with hydatidiform moles are shown in the *upper panels* of Fig. 4. The dominant peak again coeluted with marker monomeric placental lactogen and comprised 88% to 92% of total placental lactogen recovered (Table I). No distinct peak was found in the region of dimeric placental lactogen. The placental lactogen immunoactivity eluting at the void volume comprised 1.8% to 4.3% of the placental lactogen recovered.

Elution profiles of tissue extracts from these same patients are shown in the *lower panels* of Fig. 4. The placental lactogen immunoactivity eluting in the regions of monomer, dimer, and void volume comprised 95% to 97%, 1.8%, and 0.9%, respectively, of the total placental lactogen recovered (Table I). In one of the tumor extracts (Patient D. P.), there was the suggestion of an additional immunoactive species, eluting between void volume and dimeric placental lactogen (Fig. 4, *inset* to *lower left panel*).

Serum placental lactogen in patients with eutopic and ectopic malignant tumors. Only two peaks of immunoactive placental lactogen were found in the serum of a patient with metastatic gestational choriocarcinoma. As shown in the *top panel* of Fig. 5, a dominant peak eluted with marker monomeric placental lactogen (recovery of 90%, Table I), and a minor peak eluted at the void volume (recovery of 9.2%). No distinct peak was found in the region of dimeric placental lactogen. Similarly, only two peaks were found (Fig. 5, *middle* and *lower panels*) in sera of men with a retroperitoneal carcinoma and a carcinoma of the stomach. Recovery of ectopic placental lactogen was 81% to 88% for monomer and 11% to 19% for void volume (Table I). Again, no distinct peak was found in the region of dimeric placental lactogen.

First-trimester sera and placentas. Two first-trimester sera were chromatographed on Sephadex G-100. Three peaks of immunoactive placental lactogen were found. The dominant peak coeluted with marker monomeric placental lactogen and comprised 95% to 97% of the total placental lactogen recovered (Table I). The second peak (dimer) and third peak (void) comprised 0.6% to 0.7% and 0.3% to 2.5%, respectively, of total placental lactogen recovered.

Extracts of placental tissue from first-trimester abortions were chromatographed, and their elution profiles are shown in Fig. 6. As in the sera, three immunoactive placental lactogen peaks were found. As seen in the *upper panels*, the dominant peak (monomeric) comprised 93% to 99% of the total placental lactogen recovered (Table I), the second peak (dimer) <0.6% to 0.9%, and the third peak (void) <0.3% to 3.3%. Decrease in pH of the eluting buffer from 7.4 to 6.0 did not alter the amount or elution position of immunoactive void volume placental lactogen from unfractionated first-trimester placental extract (data not shown).

Immunochemical dilutions of the void volume and monomeric peaks from first-trimester placental extract No. 3 are shown in the *lower panel* of Fig. 2. Monomeric placental lactogen from this first-trimester placenta diluted in parallel to standard monomeric placental lactogen from third-trimester placenta. However, void volume placental lactogen and monomeric placental lactogen from this placenta did not dilute in parallel to each other. When void volume placental lactogen from one of these first-trimester placental extracts was rechromatographed, all immunoactivity remained at the void (Fig. 3, *lower panel*). Void volume placental lactogen from first-trimester placenta did not alter its immunologic or elution properties after storage for 11 weeks at 4° C or after dialysis against distilled water prior to lyophilization (data not shown).

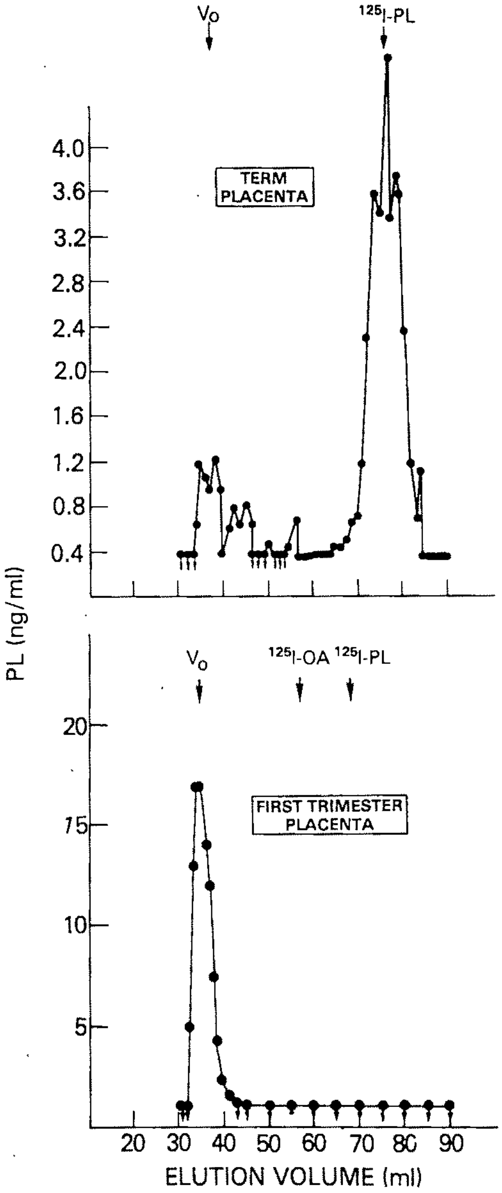

Fig. 3. Rechromatography of void volume placental lactogen on Sephadex G-100. *Upper panel:* Fractions 37 and 40 of term placental extract of B. G. (*lower right panel* of Fig. 1) were pooled and rechromatographed. *Lower panel:* Fractions 34 to 41 of first-trimester placental extract No. 3 (*upper right panel* of Fig. 6) were pooled, dialyzed against water, lyophilized, and rechromatographed.

However, in two placental extracts from the first trimester (as seen in the *lower panels* of Fig. 6), the

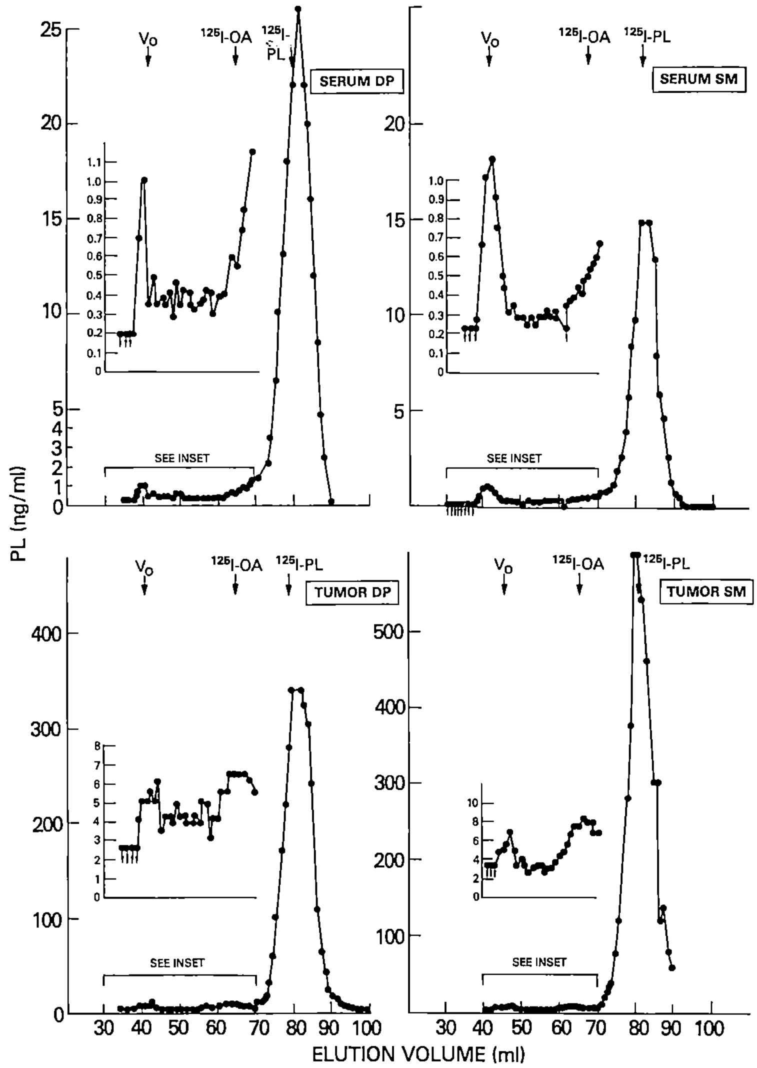

Fig. 4. Gel chromatography on Sephadex G-100 of sera and tumor extracts from patients (*DP, SM*) with hydatidiform mole. V_0 denotes the void volume, *^{125}I-OA* the elution volume of cochromatographed radioiodinated ovalbumin (molecular weight 45,000), and *^{125}I-PL* the elution volume of cochromatographed radioiodinated monomeric placental lactogen.

dominant species eluted at the void volume and comprised 44% to 46% of total placental lactogen recovered (Table I). A second species eluted in the region of dimeric placental lactogen and comprised 9.2% to 11% of the total placental lactogen recovered. The third immunoactive placental lactogen species eluted with marker monomeric placental lactogen and comprised 27% to 37% of total placental lactogen recovered.

Comment

Immunoactive placental lactogen eluting at or near the void volume of a Sephadex G-100 column (macromolecular placental lactogen) was present in all samples we examined. These included sera and placentas from term and first-trimester pregnancy, from patients with hydatidiform mole or choriocarcinoma, and from men with ectopic placental lactogen production. This macromolecular placental lactogen was probably not a laboratory artifact. We took care to process all samples promptly, under conditions designed to minimize alterations in native protein structure, and similar macromolecular forms have been reported for growth hormone[3] and for prolactin,[4] molecules that are closely related to placental lactogen.

We know little about the properties of macromolecular placental lactogen other than its large size (>150,000 daltons), its heterogeneity in certain samples (Fig. 1), its instability to rechromatography from term but not from first-trimester placentas (Fig. 3), and its immunochemical similarity to monomeric (22,000 dalton) placental lactogen (Fig. 2.). There are conflicting data in the literature on the chemistry of macromolecular forms of growth hormone and prolactin. These have variously been described as species bound to nucleic acid,[10] oligomers held together by noncovalent hydrophobic bonds,[11, 12] covalently linked polydisulfides dissociable by thiols,[12, 13] and monomers bound to protein carriers.[14] The latter suggestion has also been made in the case of macromolecular placental lactogen.[15]

Studies of the incorporation of radioactive amino acids into placental lactogen have identified a typical hydrophobic precursor piece of some 25 amino acids at the N terminus but no evidence of larger forms of pre–placental lactogen.[16] However, assessment of the products of these as of other biosynthetic experiments involves analysis on polyacrylamide gels in the presence of sodium dodecyl sulfate and a thiol, either or both of which could lead to dissociation of homopolymers or of placental lactogen bound to a carrier. In fact, in the earliest work on placental lactogen biosynthesis, Suwa and Friesen[6] used dextran gels under nondenaturing conditions to analyze the products of labeled leucine incorporation into placental lactogen by minces of placenta, and they found that macromolecular forms of placental lactogen were dominant in first-trimester tissue. We and our colleagues[17] also found high–molecular weight placental lactogen species when products of cell-free translation of messenger RNA from human placenta were analyzed under similar, nondenaturing conditions. Thus, whatever the chemical nature of these macromolecular forms, it has not yet been unequivocally established that they are posttranslational modifications of the mature protein.

We do not yet understand the pathophysiologic characteristics of macromolecular placental lactogen. This material was present to the extent of only a few percent in term serum and placenta, in first-trimester serum, and in 16 of 18 first-trimester placentas. However, it was present in amounts far exceeding those of normal pregnancy in the serum of two men with ectopic placental lactogen production by malignant neoplasms (Fig. 5). Moreover, macromolecular placental lactogen was the dominant form of placental lactogen in two of the 18 first-trimester placentas we extracted (Fig. 6.). There were no systematic differences from the other 16 in age of these placentas (4 to 9 weeks), but information about the history of the two patients, their medications, or serum protein electrophoresis is unavailable. For prolactin, a congener of placental lactogen, there are reported cases also showing predominance of a macromolecular form.[4, 18, 19] The chemistry and significance of macromolecular placental lactogen remain intriguing subjects for further investigation.

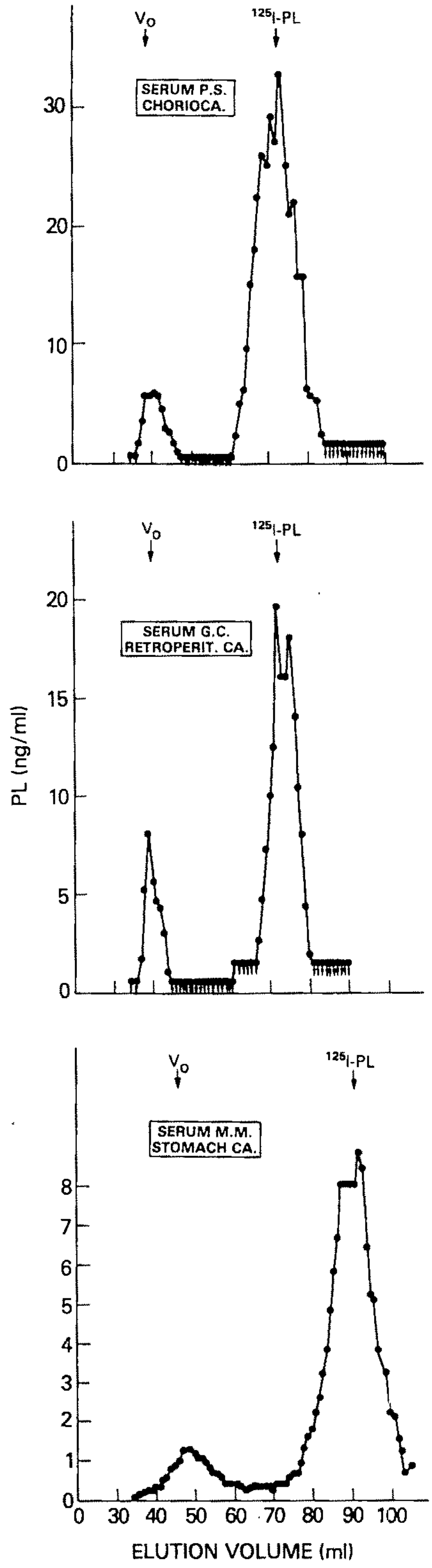

Fig. 5. Gel chromatography on Sephadex G-100 of sera from patients with choriocarcinoma, retroperitoneal carcinoma, and stomach carcinoma. V_o denotes the void volume and ^{125}*I-PL* denotes the elution volume of cochromatographed radioiodinated monomeric placental lactogen.

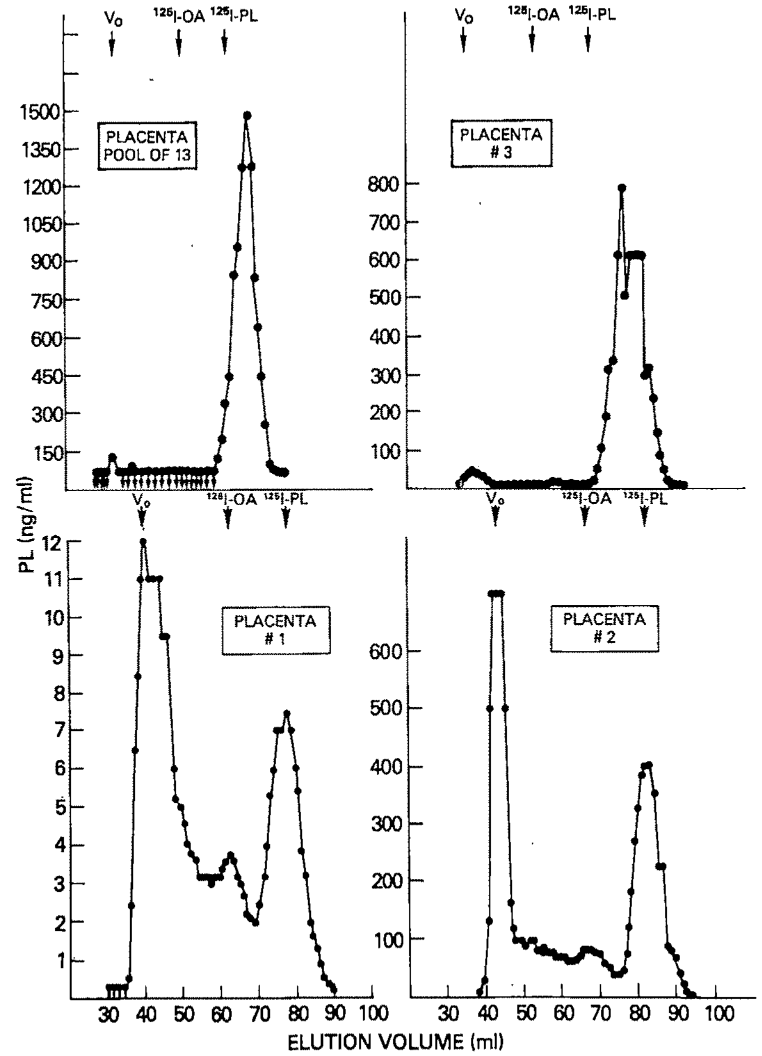

Fig. 6. Gel chromatography on Sephadex G-100 of three individual extracts and one pool extract prepared from first-trimester placentas. *V_0* denotes the void volume, *^{125}I-OA* the elution volume of cochromatographed radioiodinated ovalbumin (molecular weight 45,000), and *^{125}I-PL* the elution volume of cochromatographed radioiodinated monomeric placental lactogen.

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CORRESPONDENCE

Phospholipid analyses in amniotic fluid contaminated by seminal ejaculate

To the Editors:

With reference to the article published by Drs. Y. Romem, S. H. Golde, G. M. Mosley, and R. H. Paul, entitled "Influence of seminal ejaculate on the amniotic fluid phospholipid profile" (AM J OBSTET GYNECOL 1984;149:89) I would like to draw attention to the following points.

1. In the histogram depicting the percentage distribution of various phospholipid classes of semen, the distribution is expressed as percentage of total lipids instead of total phospholipids.
2. One of the phospholipids, *PE*, is referred to as phosphatidylethanol, instead of ethanolamine.
3. Further Jones et al.[1] have shown that human spermatozoa contain the following major phospholipid classes expressed as percentages of total phospholipids: phosphatidylcholine, 38.3%; phosphatidylethanolamine, 29.7%; sphingomyelin, 12.4%. In the article of Romem et al. it is mentioned that phosphatidylethanolamine forms only 6% to 8% of the total phospholipids in the seminal ejaculate. I have also found phosphatidylethanolamine to form one of the major phospholipid classes of seminal fluid.

The article may be written with a view to warn people about the possible risk of contamination by seminal fluid lipids in the vaginal pool which may lead to erroneous values for the lecithin/spingomyelin ratio. It will be useful in this context to do a routine microscopic analysis of the sample for seminal fluid contamination or do a qualitative test for one of the markers of seminal fluid, such as fructose, prior to amniotic fluid analysis. The article is very timely and may make people take extra precautions with respect to amniotic fluid analyses.

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REFERENCE

1. Jones R, Mann T, Sherins R. Peroxidative breakdown of phospholipids in human spermatozoa, spermicidal properties of fatty acid peroxides, and protective action of seminal plasma. Fertil Steril 1979;31:531.

Reply

To the Editors:

We appreciate Dr. Sheriff's interest in our article and are pleased with his concluding complimentary remarks.

In order to make the graph as clear as possible we have shortened the phospholipids to lipids, but the adjacent asterisk refers to the full name included in the legend. Unfortunately, phosphatidylethanolamine fell a victim to the same process, but that is the correct full name of the *PE* component.

We had not attempted to measure the phospholipid content of the spermatozoa but only of the ejaculate and seminal plasma; therefore, the comparison with the data of Jones et al. is irrelevant.

As to the percentage of phosphatidylethanolamine in the human seminal plasma the only available datum we are aware of is by Poulos and White,[1] 8.5%, which is very close to ours, 5.9% if the different methods used are taken into consideration.

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REFERENCE

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The management of bradycardia during nonstress tests

To the Editors:

The article by Bourgeois et al. (AM J OBSTET GYNECOL 1984;150:213) demonstrated the significance of profound fetal heart rate decelerations during nonstress tests. However, there are several comments in their article regarding antepartum fetal heart rate tests which must be questioned. First, the authors stated that nonreactive nonstress tests were followed by contraction stress tests. The author stated that contraction stress tests were read under "strict definition" as defined by Ray et al.[1] However, among patients demonstrating bradycardic fetal heart rate patterns with nonreactive nonstress tests the authors reported all patients had a follow-up negative contraction stress test. This is not consistent with the findings recently reported by Grundy et al.[2] These authors reviewed antepartum fetal heart rate tests performed under the direction of Dr. Freeman and report only a 0.2% incidence of truly nonreactive negative contraction stress tests. Bourgeois et al. report a 100% incidence of such tests. Second, Bourgeois et al. report interpreting some contraction stress tests as having decreased beat-to-beat variability. It must be emphasized that beat-to-beat variability cannot be interpreted on external fetal heart rate tracings. Finally, the authors state that regardless of gestational age the presence of decelerations on a nonreactive nonstress test justifies early delivery regardless of the contraction stress test findings. They state a trial of labor is justified in both instances. Again, this is not consistent with the recommendations of Freeman et al.[3] who feel that an infant demonstrating a nonreactive positive contraction stress test should be delivered abdominally without a trial of labor because of the very high incidence of fetal distress.

I agree that the significance of bradycardic episodes must be reported in the literature, however, I feel that the 25% incidence of fetal death in this series should not have occurred with a strict interpretation of contraction stress test results.

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2. Grundy H, Freeman R, Lederman S, Dorchester W. Nonreactive contraction test: clinical significance. Obstet Gynecol 1984;64:337.
3. Freeman R, Anderson G, Dorchester W: A prospective multi-institutional study of antepartum fetal heart rate monitoring. II. Contraction stress test versus nonstress for primary surveillance. AM J OBSTET GYNECOL 1982;143:778.

Reply

To the Editors:

Contraction stress tests were indeed interpreted according to "strict definition" in the patients reported. That is to say, decelerations that were not present were not counted. Since nonstress test procedures in this study were vastly different from those used in the report by Grundy et al.,[1] it comes as no surprise that the correlation between nonreactive nonstress test and negative contraction stress test was found to be different in our series.

As stated in our paper, nonstress tests were performed according to the usual method and lasted only 20 minutes. In the context of a 90-minute nonstress test, which amounts to what was performed during the contraction stress test by Grundy et al., one would expect to find a very low incidence of negative contraction stress tests. Fetal nonreactivity that persists as long as 90 minutes is more ominous than that persisting 20 minutes, as noted by Brown,[2] and would be likely correlated with positive contraction stress tests. Since the contraction stress tests were properly interpreted in these few instances, it is doubtful whether any other degree of "strict" interpretation could have changed the outcome. Recognition of the importance of the deceleration would have.

Fetal heart rate baseline variability on external monitors is uninterpretable when it appears to be "normal." Since external monitors, if anything, exaggerate the appearance of beat-to-beat variability, the observation of diminished variability can and should be interpreted as significant.

With regard to the method of delivery of the compromised fetus, variations between our recommendation and those of other authors must be resolved by the individual reader.

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REFERENCES

1. Grundy H, Freeman R, Lederman S, Dorchester W. Nonreactive contraction test: clinical significance. Obstet Gynecol 1984;64:337.
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HELLP syndrome: Pathologic entity or technical inadequacy?

To the Editors:

Recently a syndrome characterized by hemolysis, elevated liver enzymes, and low platelet count (HELLP) has been described in patients with preeclampsia (Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. AM J OBSTET GYNECOL 1982;142:159-167). This is apparently regarded as a separate disease entity, which is associated with preeclampsia. The classification of hypertension in pregnancy is already complex and without good evidence should not be further complicated by the addition of a syndrome such as HELLP.

Preeclampsia has long been known to be associated with disseminated intravascular coagulation,[1, 2] which is characterized by microangiopathic hemolytic anemia, platelet consumption, and activation of coagulation and fibrinolytic pathways. Liver function abnormalities are known to occur both in disseminated intravascular coagulation and in preeclampsia.[3] Weinstein does not consider the HELLP syndrome to be disseminated intravascular coagulation, since coagulation parameters such as prothrombin time, partial thromboplastin time, and fibrinogen are normal. However, these parameters have low sensitivities for the changes of disseminated intravascular coagulation seen in preeclampsia. It has been shown that the prothrombin time, partial thromboplastin time, and fibrinogen may not be significantly different from normal in severe preeclampsia, despite significant changes in Factor VIII, plasminogen, and antithrombin III.[1] Furthermore, studies using more sensitive indices of coagulation activation such as soluble fibrinogen-fibrin complexes[4] and fibrinopeptide A[5] have been shown to be abnormal in preeclampsia, and even more sensitive indices of fibrinogen-fibrin breakdown such as assays for B-B-15-42 and D-dimer fragments are now available.

We would suggest that the HELLP syndrome is in fact mild disseminated intravascular coagulation associated with preeclampsia, and that this syndrome has arisen because of technical inadequacy, since sensitive measurements of coagulation activation have not been employed in the evaluation of these patients.

The HELLP syndrome does not therefore merit separate consideration from preeclampsia, and the term should be abandoned before it leads to further confusion in the understanding and treatment of the disease.

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The elusive ellipse

To the Editors:

We noticed several errors in the article entitled "Choosing the correct equation for computing the head circumference from two diameters" (DeVore GR, Platt LD. AM J OBSTET GYNECOL 1984;148:221). The authors compared a commonly used equation for obtaining the head circumference to an equation they stated was the correct calculation for the true circumference of an ellipse.

Unfortunately, the reference used[1] does not supply the correct expression. The equation is only one of many approximations of the true circumference of an ellipse and is not necessarily the best one. The true circumference of an ellipse can only be found by use of an expression called the elliptic integral, which appears as follows[2]:

$$\text{Circumference} = 4\int_0^{\frac{\pi}{2}} \sqrt{a^2\cos^2\phi + b^2\sin^2\phi}\, d\phi$$

$$= 4a\int_0^{\frac{\pi}{2}} \sqrt{1\text{-}e^2\sin^2\phi}\, d\phi = 4aE = 2D_2E(m_1)$$

where D_2 = major axis of an ellipse; D_1 = minor axis of an ellipse; $a = \frac{1}{2}$(major axis), or semimajor axis; $b = \frac{1}{2}$(minor axis), or semiminor axis; $e = \sqrt{a^2 - b^2}/a$, the eccentricity of the ellipse; $m_1 = D_1^2/D_2^2$, the complementary parameter of the elliptic integral; ϕ = the angle between the radius vector and the positive y axis; E = the elliptic integral.

As can be seen, this expression is difficult to use. There are several infinite expansion series for E, but no exact value can be found for this integral, just as the exact value of pi cannot be found. There are, however, several good approximations correct to several decimal places. Here is one such approximation.[2]

$$E(m_1) = (1 + a_1m_1 + a_2m_1^2) + (b_1m_1 + b_2m_1^2)\ln(1/m_1) + \epsilon(m), |\epsilon(m)| < 4 \times 10^{-5}$$

$$a_1 = 0.4630151 \qquad b_1 = 0.2452727$$
$$a_2 = 0.1077812 \qquad b_2 = 0.0412496$$

In obstetrics the cephalic index is the ratio of biparietal diameter to the occipitofrontal diameter. It has an approximate range from 0.7 to 0.9, depending on the degree of head compression. If the head is compared to an ellipse, the biparietal diameter can be represented by D_1 and the occipitofrontal diameter by D_2, which would fall along the minor and major axes of an ellipse.

For purposes of comparison, let us call the approximation $E(m_1) \times 2D_2$, accurate to four decimal places, the "true" circumference. We can then compare computed values over the range of minor/major axis ratio from 0.7 to 1.0 for the "true" circumference to other approximations. In addition to the two equations evaluated by Drs. DeVore and Platt, two additional approximations of the circumference of an ellipse can be derived by noting that the plot of the ratio of the minor/major axes from 0.7 to 1.0 versus the "true" circumference of an ellipse is nearly linear. The four equations that can now be used to approximate the circumference of an ellipse are as follows:

$$\frac{\pi}{2}(D_1 + D_2) \tag{1}$$

$$4.443\sqrt{(D_1^2/2) + (D_2^2/2)}, \text{ or } \pi\sqrt{(D_1^2 + D_2^2)/2} \tag{2}$$

$$1.58\,(D_1 + D_2) \tag{3}$$

$$1.5\,(D_1) + 1.64\,(D_2) \tag{4}$$

Table I compares the computed values of each approximation to the "true" circumference, over a minor/major axis ratio from 0.70 to 1.00. A linear regression was computed for each comparison, and the r value given. Table II lists the percentage difference from the "true" circumference over the same range of minor/major axis ratio.

It can be seen that all four equations approximate the "true" circumference quite well. Equations 1 and 2 perform equally well over the range of interest. Although the calculations will not be presented, this relationship holds true to the minor/major axis ratio of 0.5, with a maximum percent error of 2.7% for equation 1. Equations 3 and 4 have uniformly small errors.

Which equation to use? Arriving at an accurate estimate of the circumference of an ellipse is not difficult. Stating that the fetal head is an ellipse is another matter. Recent work has shown that to measure the head circumference with a mapreader, or digitizer, or to calculate it from diameters will yield results that are sim-

Table I. Circumference of an ellipse with unit major axis length

Ratio of minor/major axes	*"True" circumference*	*Equation**			
		1	*2*	*3*	*4*
0.7000	2.6911	2.6703	2.7116	2.6860	2.69
0.7200	2.7196	2.7017	2.7373	2.7176	2.72
0.7400	2.7483	2.7331	2.7635	2.7492	2.75
0.7600	2.7774	2.7646	2.7901	2.7808	2.78
0.7800	2.8066	2.7960	2.8172	2.8124	2.81
0.8000	2.8361	2.8274	2.8448	2.8440	2.84
0.8200	2.8658	2.8588	2.8727	2.8756	2.87
0.8400	2.8957	2.8902	2.9011	2.9072	2.90
0.8600	2.9258	2.9216	2.9299	2.9388	2.93
0.8800	2.9561	2.9530	2.9591	2.9704	2.96
0.9000	2.9866	2.9845	2.9886	3.0020	2.99
0.9200	3.0173	2.0159	3.0185	3.0336	3.02
0.9400	3.0481	3.0473	3.0488	3.0652	3.05
0.9600	3.0791	3.0787	3.0794	3.0968	3.08
0.9800	3.1102	3.1101	3.1103	3.1284	3.11
1.0000	3.1415	3.1415	3.1415	3.1600	3.14
		r = 0.9999	r = 0.9999	r = 0.9999	r = 0.9999

*See text for equation.

Table II. Percent error of each equation

Ratio of minor/major axes	*Equation**			
	1	*2*	*3*	*4*
0.7000	−0.7711	0.7620	−0.1897	−0.04
0.7200	−0.6565	0.6511	−0.0745	0.01
0.7400	−0.5535	0.5505	0.0291	0.06
0.7600	−0.4613	0.4598	0.1218	0.09
0.7800	−0.3794	0.3785	0.2042	0.12
0.8000	−0.3071	0.3063	0.2769	0.14
0.8200	−0.2440	0.2426	0.3404	0.15
0.8400	−0.1893	0.1872	0.3954	0.15
0.8600	−0.1427	0.1397	0.4423	0.14
0.8800	−0.1036	0.0996	0.4816	0.13
0.9000	−0.0715	0.0667	0.5139	0.11
0.9200	−0.0459	0.0407	0.5397	0.09
0.9400	−0.0264	0.0213	0.5593	0.06
0.9600	−0.0125	0.0083	0.5732	0.02
0.9800	−0.0039	0.0012	0.5820	−0.01
1.0000	0.0000	0.0000	0.5859	−0.05

*See text for equation.

ilar.[3, 4] Measurement errors from observer to observer range up to about 3%. The error introduced by assuming the head is an ellipse and using any of the four equations examined is much less than reported measurement errors. We conclude that the practitioner may with equal confidence measure the circumference of the fetal head either directly or indirectly via diameters and any of the four equations.

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4. Stempel LE. Estimation of fetal weight using real-time ultrasound. Presented at the twenty-eighth annual meeting of the Society for Gynecological Investigation, St. Louis, March 18-21, 1981.

Reply

To the Editors:

In response to Drs. Christenson and McCown, we would like to point out the following:

1. The purpose of our communication was to illustrate that the equation for computing the circumfer-

ence of a circle [(D1 + D2) 1.57] was clinically useful when deriving gestational age from the head circumference except when an abnormal cephalic index of <79% with a biparietal diameter >7 cm.

2. We take no credit for the "correctness" of the equation for the circumference of an ellipse. This was the reason for referring to *Scientific Tables.* We can only assume that the editors of this particular reference thought that there was no difference between the equation for the circumference of an ellipse which they used and the "true equation" referred to by the authors of the above letter.

3. Our only criticism of the above letter is that the authors did not represent their data in a similar format as illustrated in Fig. 2 of our article, for it can be seen that for a given cephalic index, the error in estimating gestational age from the head circumferences increases as the biparietal diameter increases. If they had done this, perhaps they might have been more revealing as to the clinical significance of their communication.

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Mumps and postmenopausal ovarian cancer

To the Editors:

In the article entitled "Mumps, menarche, menopause, and ovarian cancer" (Cramer DW, Welch WR, Cassells S, Scully RE. AM J OBSTET GYNECOL 1983; 147:1-6) Cramer et al. suggest that mumps infection may increase the risk of postmenopausal ovarian cancer via a causal chain thought to include inapparent oophoritis, oocyte depletion, and resultant premature menopause. They present evidence from a case-control interview study to support their hypothesis, which they outline more fully in another publication.[1]

We have attempted to reproduce the findings of Cramer et al. in data collected as part of a similar case-control interview study of ovarian cancer. Our case series included 298 women with pathologically confirmed primary ovarian cancer of the epithelial type who were treated at 33 participating hospitals in the Washington, D. C., area. The controls were 344 women treated at the same hospitals for conditions presumed to be unrelated to the exposures under study. Excluded conditions included gynecologic disease, gallbladder complaints, ischemic cardiovascular disease, colon cancer, melanoma, and pregnancy. The controls were frequency-matched to cases on age, race, and hospital. To promote comparability with the study of Cramer et al., we have restricted the present analysis to 147 white case women reporting a natural menopause and to 152 corresponding control women.

In Table I, mumps history data from the two studies are presented for comparison. Cramer et al. found a significant excess of uncertain mumps histories among their case women compared to controls. They postulated that this excess might represent increased inapparent mumps oophoritis among cases. In contrast, our subjects were much more certain of their mumps history than were the subjects of Cramer et al. Among the few women who could not recall whether they had had mumps, cases and controls were equally represented. These two observations argue against the importance of an "uncertain" mumps history.

We did find, in agreement with Cramer et al., that among subjects reporting a positive mumps history, more cases (20%) than controls (13%) were initially unsure of their age at exposure. However, in our study a follow-up question allowed these subjects to date their mumps history more broadly, using four age categories. The group unable to date their exposure was reduced to only five (three cases, 2 controls). The explanation for this finding is unclear; overall, we believe that an uncertain mumps history is more likely to be a result of interviewing method than a suggestion of inapparent mumps infection.

As part of their hypothesis, Cramer et al. suggest that silent mumps infection causes premature ovarian failure. Our data do not support this conclusion. Control women with a negative or uncertain mumps history reported a later average menopause (49.3 ± 0.5) than control women with a positive mumps history (48.7 ± 0.5).

Cramer et al. found a significant negative correlation

Table I. Clinical history of mumps for postmenopausal case subjects with ovarian cancer and for corresponding control subjects in two studies

	Washington, D.C., case-control study				*Cramer et al. (1983)*			
	Cases		*Controls*		*Cases*		*Controls*	
Clinical history of mumps	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Negative								
Never had	41	27.9	38	25.0	26	21.9	24	22.0
Unknown whether had	9	6.1	10	6.6	33	27.7	17	15.6
Positive								
Had, age known	67	45.6	85	55.9	10	8.4	30	27.5
Had, age unknown	30	20.4	19	12.5	50	42.0	38	34.9
Total	147	100.0	152	100.0	119	100.0	109	100.0

between age at menarche and age at menopause among both case and control women who recalled having had mumps. In contrast, we observed a nonsignificant positive correlation in both groups. The strongest negative correlation seen by Cramer et al. was among nulliparous white case women who recalled having mumps; among the 24 subjects in this subgroup we found a significant (p = 0.001) positive Pearson's correlation coefficient of 0.62. Our correlational results, combined with those of Cramer et al., suggest that the significant correlations found in either study may represent artifactual findings caused by extensive subgroup analysis.

In summary, our results do not support the hypothesis of Cramer et al. However, we agree with the authors that mumps history is an inadequate measure of exposure. To further clarify the relation of mumps infection to ovarian cancer, serologic techniques such as enzyme-linked immunosorbent assay must be used. Of course, even when accurate serologic techniques are used, oophoritis caused by inapparent mumps infection remains an unmeasurable entity, so this aspect of the hypothesis by Cramer et al. cannot be tested at present.

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Reply

To the Editors:

Table I compares the results of published case-control studies[1-4] on the relationship of clinical history of mumps parotitis and ovarian cancer with the data offered by Schiffman et al. Two points are worthy of comment. First, all of the studies demonstrate an excess of controls over cases who have a positive clinical history of mumps parotitis and conversely an excess of cases over controls with a negative clinical history. An earlier study by West[5] also reported this finding (with a statistical significance of 0.007), but details on the numbers and proportions were not provided. The second point is that the data of Schiffman et al. stands out as having the smallest difference between cases and controls, 2% compared to the 10% to 18% found in the other studies. The atypicality of their data in this respect should be considered in weighing the evidence against the mumps hypothesis offered by their data.

Perhaps Schiffman et al. are correct in their assertion that the association of mumps history with ovarian cancer is a result of interviewer bias, but the fact that repeated independent studies have found differences suggests to us that the association is real. We certainly concede that clinical history of mumps is an inadequate measure of a woman's actual experience with mumps. Like Schiffman et al., we despair that case-control studies, even with use of sensitive antibody studies, will ever be able to distinguish past oophoritis from parotitis. Perhaps the best we can hope for is that a suitable animal model may be found to demonstrate the long-term effect of mumps on ovaries.

In conclusion, the data presented by Schiffman et al. do not compel us to change the major elements of our hypothesis, which were as follows: (1) Women with ovarian cancer differ in some way in their past experience with mumps infection from other women. (2) A possible interpretation of this difference is that women with ovarian cancer have more frequently suffered unapparent mumps oophoritis. (3) Since mumps oophoritis has been linked to premature ovarian failure, the mumps virus could be linked to ovarian cancer in the

Table I. Comparison of case-control studies* on the relationship of clinical history of mumps parotitis and ovarian cancer with the data of Schiffman et al.

	Positive clinical history				*Negative clinical history*			
	Cases		*Controls*		*Cases*		*Controls*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Newhouse et al.[1]	128	43	318	53	172	57	282	47
Menczer et al.[2]	25	36	29	49	44	64	30	51
Golan et al.[3]	13	38	19	56	21	62	15	44
Cramer et al.[4] (postmenopausal subjects)	60	50	68	62	59	50	41	38
Shiffman et al. (postmenopausal subjects)	97	66	104	68	50	34	48	32

*Numbers of subjects inferred from proportions stated in text.

same way that agents that induced ovarian failure in animals also produced ovarian tumors.

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Erratum

In the April 1, 1984, issue of the JOURNAL, in the article by Fabro, McLachlan, and Dames, entitled "Chemical exposure of embryos during the preimplantation stages of pregnancy: Mortality rate and intrauterine development," on page 929, the following footnotes should have appeared:

A large portion of this work was carried out in the Department of Pharmacology, The George Washington University Medical Center, Washington, D. C., and was supported by United States Public Health Service Research Grant GM13749 from the National Institute of General Medical Sciences, National Institutes of Health. J. A. M. and N. M. D. were trainees supported by Training Grant GM26.

Portions of this work are from a dissertation by J. A. M. and a thesis by N. M. D. presented to the Department of Pharmacology, The George Washington University Graduate School of Arts and Sciences, in partial fulfillment of the requirements for the Ph.D and M.S. degrees, respectively.

Books received

An Introduction to Recombinant DNA. Alan E. H. Emery. 223 pages, illustrated. Somerset, New Jersey, 1984, John Wiley & Sons. $17.95 (soft cover).

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Ultrasound Mammography. Edited by Pat Harper. 224 pages, illustrated. Baltimore, 1984, University Park Press. $39.50.

Announcements of major meetings and other significant activities must be received at least 8 weeks before the desired month of publication. All announcements carry a charge of $45.00 U.S. and the fee must accompany the request to publish. Information will be limited to title of meeting, date, place, and an address to obtain further information. Send announcements and payment, payable to this JOURNAL, to The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63146.

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Issues in Maternal-Fetal Medicine: Teratology, Principles and Clinical Applications, July 27–August 1, 1985, Snowmass, Colorado. For further information contact: CME Office, Texas A&M University College of Medicine, Scott and White, Temple TX 76508. Tel.: (817) 774-2350.

London and Paris Fall Ultrasound—Obstetrics and Gynecology, London, England, September 20-25, 1985; Paris, France, September 25-29, 1985. For further information contact: Secretary, Fall Ultrasound Symposia, Medical Seminars International, West Park Medical Office Building, 22135 Roscoe Blvd., #104, Canoga Park, CA 91304. Tel.: (818) 340-0580, ext. 280.

Birth Defects Symposium XVI, Genetic Disease Screening and Management, September 30–October 1, 1985, Albany Hilton Hotel, Albany, New York. For further information contact: Thomas P. Carter, Ph.D., Wadsworth Center for Labs and Research, Rockefeller Empire State Plaza, Albany, NY 12201.

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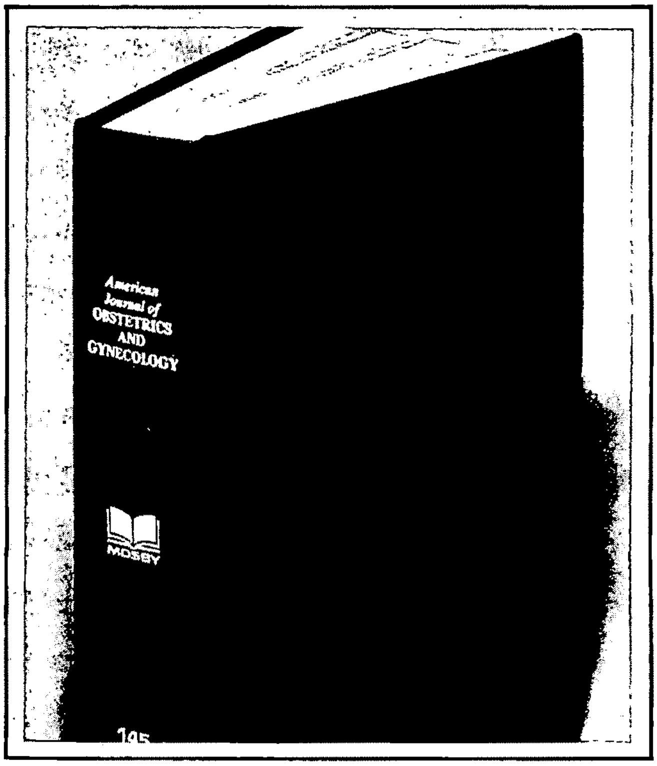

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Ogen 27A,28A,29A,35A,36A,37A

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Fetal Scalp Electrode 3A

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Bristol-Myers Company
Nuprin Medical 32A,33A

Carle Clinic
Opportunity Available 42A

Compliance Systems Corporation
Pill Dispenser 8A

Georgetown University Hospital
Opportunity Available 42A

Group Health, Inc.
Opportunity Available 43A

Institute for Applied Laser Surgery, The
Course 43A

Jobst
Vairox 30A,31A

Johns Hopkins Medical Institutions, The
Course 42A

Longmont Clinic, P.C.
Opportunity Available 33A

Louisiana State University Medical Center
Opportunity Available 33A

Magee-Womens Hospital
Opportunity Available 42A

Memorial Hospital, The
Opportunity Available 44A

Mosby Company, The C.V.
Books 22A

National Medical Enterprises
Opportunity Available 43A

Ortho Pharmaceutical Corporation
Ortho-Novum 7/7/7 .. Third Cover,Fourth Cover

Pennsylvania Hospital
Opportunity Available 32A

Purdue Frederick
Betadine 6A

Roerig
Cefobid 14A,15A,16A

Southern Illinois University School of Medicine
Opportunity Available 44A

St. John's Mercy Medical Center
Opportunity Available 45A

Surgipath Medical Industries, Inc.
Surgi-Pap Kit 12A

Syntex Laboratories, Inc.
Tri-Norinyl Second Cover,1A,2A

Temple University
Opportunity Available 44A

University of Illinois College of Medicine
Fellowship 32A

University of Massachusetts Medical Center
Opportunity Available 45A

University of Tennessee
Opportunity Available 45A

Ventrex Laboratories, Inc.
Ventrescreen 4A

Women & Infants Hospital
Opportunity Available 45A

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WARNINGS

> **Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke. The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.**

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. Overall excess mortality due to pulmonary embolism or stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age. **CEREBROVASCULAR DISORDERS:** In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than in nonusers. A prospective study conducted in Great Britain estimated that former users have a risk for all cerebrovascular disease 2.6 times greater than that of nonusers. This risk remained elevated for at least six years after last oral contraceptive use. A prospective study conducted in the United States found that past use of oral contraceptives was associated with increased risk of subarachnoid hemorrhage, the relative risk being 5.3. There was also some evidence from this study that the degree of risk may be related to duration of oral contraceptive use. **MYOCARDIAL INFARCTION:** An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30-39 age group and 67 cases per 100,000 women users in the 40-44 age group. In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent. A study suggests that some increased risk of myocardial infarction in oral contraceptive users persists following discontinuation of oral contraceptives and that the degree of the residual risk is related to the duration of the past use. **Risk of Dose:** In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives. Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only oral contraceptives have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age. Oral contraceptives are, however, an independent risk factor for these events. **ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES:** A large prospective study carried out in the United Kingdom estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous versus intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. This study reports that the increased risk of circulatory disease mortality may persist after the pill is discontinued. Another study published at the same time confirms a previously reported increase of mortality in pill users from cardiovascular disease. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers [more than 15 cigarettes a day], the rates given would be about double; for "light" smokers [less than 15 cigarettes a day], about 50 percent.) The mortality associated with oral contraceptive use in nonsmokers over 40 is higher than with any other method of contraception in that age group. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of postsurgery thromboembolic complications has been reported in oral contraceptive users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2. OCULAR LESIONS. There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures. 3. CARCINOMA. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on oral contraceptives. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occurred in women who had used a sequential oral contraceptive. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives. Several studies have found no increases in breast cancer in women taking oral contraceptives or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of oral contraceptives has been well-documented. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. 4. HEPATIC TUMORS. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study showed that oral contraceptive formulations with high hormonal potency were associated with a higher risk than lower potency formulations and use of oral contraceptives with high hormonal potency and age over 30 years may further increase the woman's risk of hepatocellular adenoma. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of oral contraceptives. Two studies relate risk with duration of use of the contraceptive, the risk being much greater after four or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time. 5. USE IN OR IMMEDIATELY PRECEDING PREGNANCY, BIRTH DEFECTS IN OFFSPRING, AND MALIGNANCY IN FEMALE OFFSPRING. The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be on the order of 1 to 4 in 1000 exposures. Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy. One case control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if the progestogen-only oral contraceptives are used), and further use of oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months although no precise information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. GALLBLADDER DISEASE. Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and estrogens. In one study, an increased risk appeared after two years of use and doubled after four or five years of use. In one of the other studies, an increased risk was apparent between six and twelve months of use. 7. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives. The clinical significance of this finding remains to be defined. 8. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug. 9. HEADACHE. The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause. 10. BLEEDING IRREGULARITIES. Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Postuse anovulation, possibly prolonged, may also occur in women without previous irregularities. 11. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. 12. BREAST FEEDING. Oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast-fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned. **PRECAUTIONS: General:** 1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. 4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8. Serum folate levels may be depressed by oral contraceptive therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. **INFORMATION FOR THE PATIENT: (See Patient Package Insert). DRUG INTERACTIONS:** Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin, griseofulvin, and tetracycline. **CARCINOGENESIS, PREGNANCY, NURSING MOTHERS: See CONTRAINDICATIONS and WARNINGS. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis. Pulmonary embolism. Coronary thrombosis. Cerebral thrombosis. Cerebral hemorrhage. Hypertension. Gallbladder disease. Liver tumors. Congenital anomalies. There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis. Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, usually the most common adverse reaction. Vomiting occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Dysmenorrhea. Amenorrhea during and after treatment. Temporary infertility after discontinuance of treatment. Edema. Chloasma or melasma which may persist. Breast changes: tenderness, enlargement, and secretion. Change in weight (increase or decrease). Change in cervical erosion and cervical secretion. Possible diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Increase in size of uterine leiomyomata. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome. Cataracts. Changes in libido. Chorea. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. Hemolytic uremic syndrome. **OVERDOSAGE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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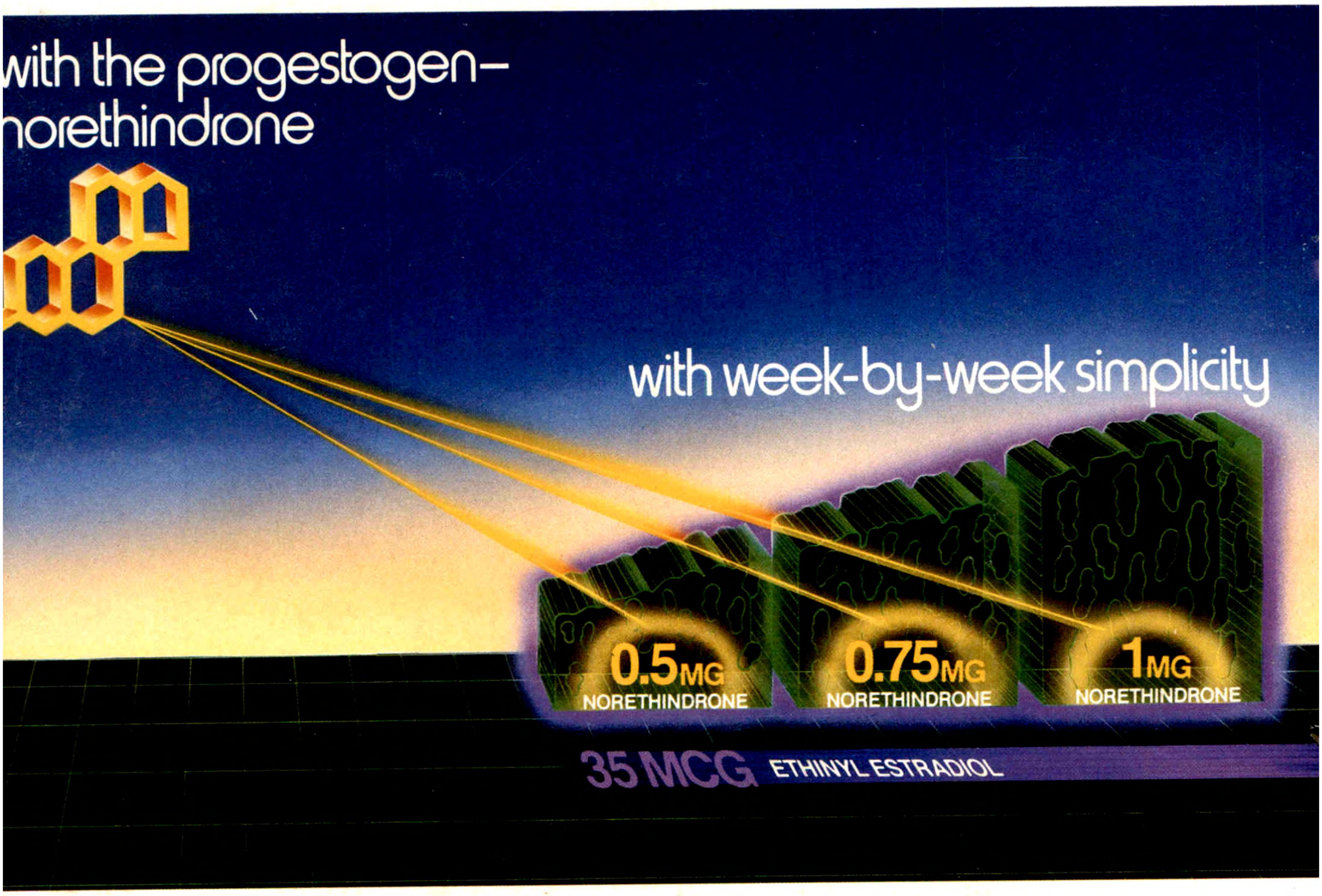

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Contents

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TRANSACTIONS OF THE FIFTY-SECOND ANNUAL MEETING OF THE CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

"Is That All There Is?" 139
Kenneth J. Vander Kolk, M.D.
Grand Rapids, Michigan

Vaginal breech delivery of selected infants weighing more than 2000 grams 145
Robert K. Tatum, M.D., James W. Orr, M.D., Seng-jaw Soong, Ph.D., and
John J. Huddleston, M.D.
Birmingham, Alabama

Flow velocity waveforms in the maternal uteroplacental and fetal umbilical placental circulations 155
Brian J. Trudinger, M.B., Warwick B. Giles, M.B., and
Colleen M. Cook, R.N.
Westmead, Australia

(Contents continued on page 4A)

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Contents continued from page 3A

A Circle and the Eight Happinesses 163
John M. Beazley, M.D.
Liverpool, England

Long-term use of intrauterine contraceptive devices in a private practice 169
Herbert F. Sandmire, M.D., and Robert A. Cavanaugh, M.D.
Green Bay, Wisconsin

The midforceps: Maternal and neonatal outcomes 176
LeRoy J. Dierker, Jr., M.D., Mortimer G. Rosen, M.D., Karen Thompson, Sara Debanne, Ph.D., and Patricia Linn, Ph.D.
Cleveland, Ohio

Eclampsia. IV. Neurological findings and future outcome 184
Baha M. Sibai, M.D., Joseph A. Spinnato, M.D., Dottie L. Watson, M.D., James A. Lewis, M.D., and Garland D. Anderson, M.D.
Memphis, Tennessee

Cervicography: A preliminary report 192
James G. Blythe, M.D.
St. Louis, Missouri

Is intraperitoneal dextran 70 safe for routine gynecologic use? 198
David M. Magyar, D.O., Maria F. Hayes, M.D., Nicholas J. Spirtos, D.O., Magdalen E. Hull, M.D., and Kamran S. Moghissi, M.D.
Detroit, Michigan

Chorionic villus sampling for first-trimester prenatal diagnosis: Northwestern University Program 204
Sherman Elias, M.D., Joe Leigh Simpson, M.D., Alice O. Martin, Ph.D., Rudy E. Sabbagha, M.D., Albert B. Gerbie, M.D., and Louis G. Keith, M.D.
Chicago, Illinois

Noninvasive prediction of hyaline membrane disease: An optimized classification of sonographic placental maturation. 213
George M. Kazzi, M.D., Thomas L. Gross, M.D., Robert J. Sokol, M.D., and S. Nadya J. Kazzi, M.D.
Detroit, Michigan, and Cleveland, Ohio

Office hysteroscopy and suction curettage: Can we eliminate the hospital diagnostic dilatation and curettage? 220
Milton H. Goldrath, M.D., and Alfred I. Sherman, M.D.
Detroit, Michigan

Contents

Second-look laparotomy in ovarian cancer: Evaluation of pathologic variables 230
Karl C. Podratz, M.D., Ph.D., George D. Malkasian, Jr., M.D., Joan F. Hilton, M.P.H., Elizabeth Ann Harris, M.D., and Thomas A. Gaffey, M.D.
Rochester, Minnesota

Maternal weight and pregnancy complications 238
John A. Garbaciak, Jr., M.D., Michael Richter, M.D., Steve Miller, M.S., and John J. Barton, M.D.
Chicago, Illinois

ITEMS

Items 246

ERRATA

Correction of article by Naden, Gant, and Rosenfeld 219

Addition to list of consultants 229

Information for authors on pages 15A and 16A

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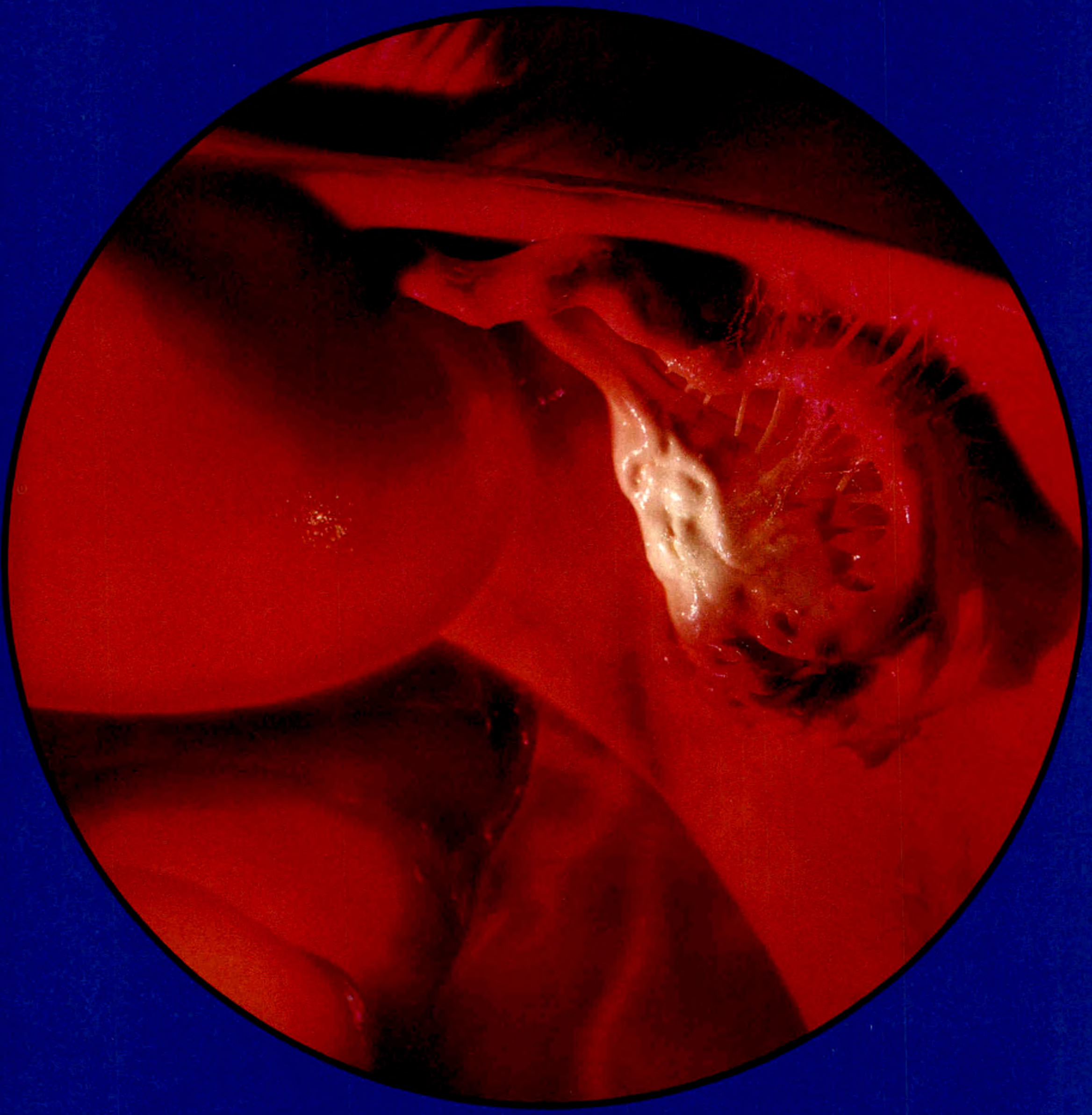

Artist's concept of the uterus
and adnexa as viewed through
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after 6 years the facts *still* favor Mefoxin® IV/IM

(Cefoxitin Sodium|MSD

MEFOXIN is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics. Before therapy with MEFOXIN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefoxitin, cephalosporins, penicillins, or other drugs. This product should be given with caution to penicillin-sensitive patients.

- **proven highly effective**
  Over 65 clinical studies document the effectiveness of MEFOXIN in the treatment of gynecological infections, including endometritis, pelvic cellulitis, and pelvic inflammatory disease.

- **proven stability**
  MEFOXIN has become the reference standard for stability against beta-lactamases which destroy other antibiotics.

- **proven utility**
  Current survey data show that obstetricians/gynecologists rely on MEFOXIN for the hospital treatment of pelvic infections more often than any other single injectable antibiotic.

  Over 6 years of use in hospitals confirms MEFOXIN has a safety profile comparable to cephalothin. The most common adverse reactions have been local reactions following intravenous or intramuscular injection.

For a Brief Summary
of Prescribing Information,
please see following page.

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Mefoxin® IV/IM (Cefoxitin Sodium | MSD)

Indications and Usage: ***Treatment***—Serious infections caused by susceptible strains of the designated microorganisms in the following diseases:
LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), other streptococci (excluding enterococci, e.g., *Strep. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Hemophilus influenzae*, and *Bacteroides* species.
GENITOURINARY INFECTIONS. Urinary tract infections caused by *E. coli*, *Klebsiella* species, *Proteus mirabilis*, indole-positive *Proteus* (i.e., *P. morganii*, *P. rettgeri*, and *P. vulgaris*), and *Providencia* species. Uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing).
INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ and *Clostridium* species.
GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by *E. coli*, *N. gonorrhoeae* (penicillinase and non-penicillinase producing), *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and group B streptococci.
SEPTICEMIA caused by *Strep. pneumoniae* (formerly *D. pneumoniae*), *Staph. aureus* (penicillinase and non-penicillinase producing), *E. coli*, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.§
BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).
SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to cefoxitin.

Contraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, from mild to life-threatening in severity, has been reported with virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis when diarrhea develops in association with antibiotic use. Broad-spectrum antibiotics alter normal flora of colon and may permit overgrowth of clostridia; a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis. Mild cases may respond to drug discontinuance alone; in more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and use of a drug such as oral vancomycin; isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: Total daily dose should be reduced in patients with reduced urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur from usual doses. Prescribe with caution in patients with a history of gastrointestinal disease, particularly colitis. Prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures. Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Interference with Laboratory Tests—High concentrations (>100 mcg/ml) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. High concentrations may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction and produce false increases of modest degree in levels reported. A false-positive reaction for glucose in urine has been observed with CLINITEST‖ reagent tablets.

Pregnancy—In women of childbearing potential, weigh anticipated benefit against possible risks.

Nursing Mothers—Cefoxitin is excreted in human milk in low concentrations.

Infants and Children—Safety and efficacy in infants from birth to three months have not yet been established. In children three months and older, higher doses have been associated with increased incidence of eosinophilia and elevated SGOT.

Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reactions*—Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. *Allergic Reactions*—Rash (including exfoliative dermatitis), pruritus, eosinophilia, fever, and other allergic reactions. *Gastrointestinal*—Symptoms of pseudomembranous colitis during or after treatment and, rarely, nausea and vomiting. *Blood*—Transient eosinophilia, leukopenia, neutropenia, hemolytic anemia, and thrombocytopenia; a positive direct Coombs test may develop in some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase. *Renal Function*—Elevations in serum creatinine and/or blood urea nitrogen levels and, rarely, acute renal failure.

Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. The total daily dosage in infants and children should not exceed 12 grams.

How Supplied: Sterile cefoxitin sodium in vials and infusion bottles containing 1 gram or 2 grams cefoxitin equivalent and in 10-gram bulk bottles.

§B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus

‖Registered trademark of Ames Company, Division of Miles Laboratories, Inc.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486

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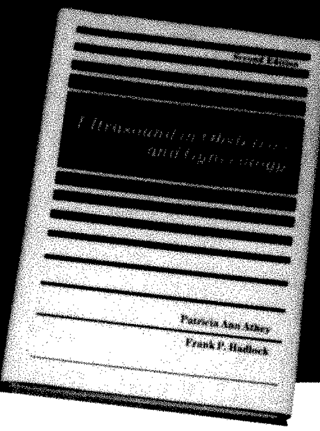

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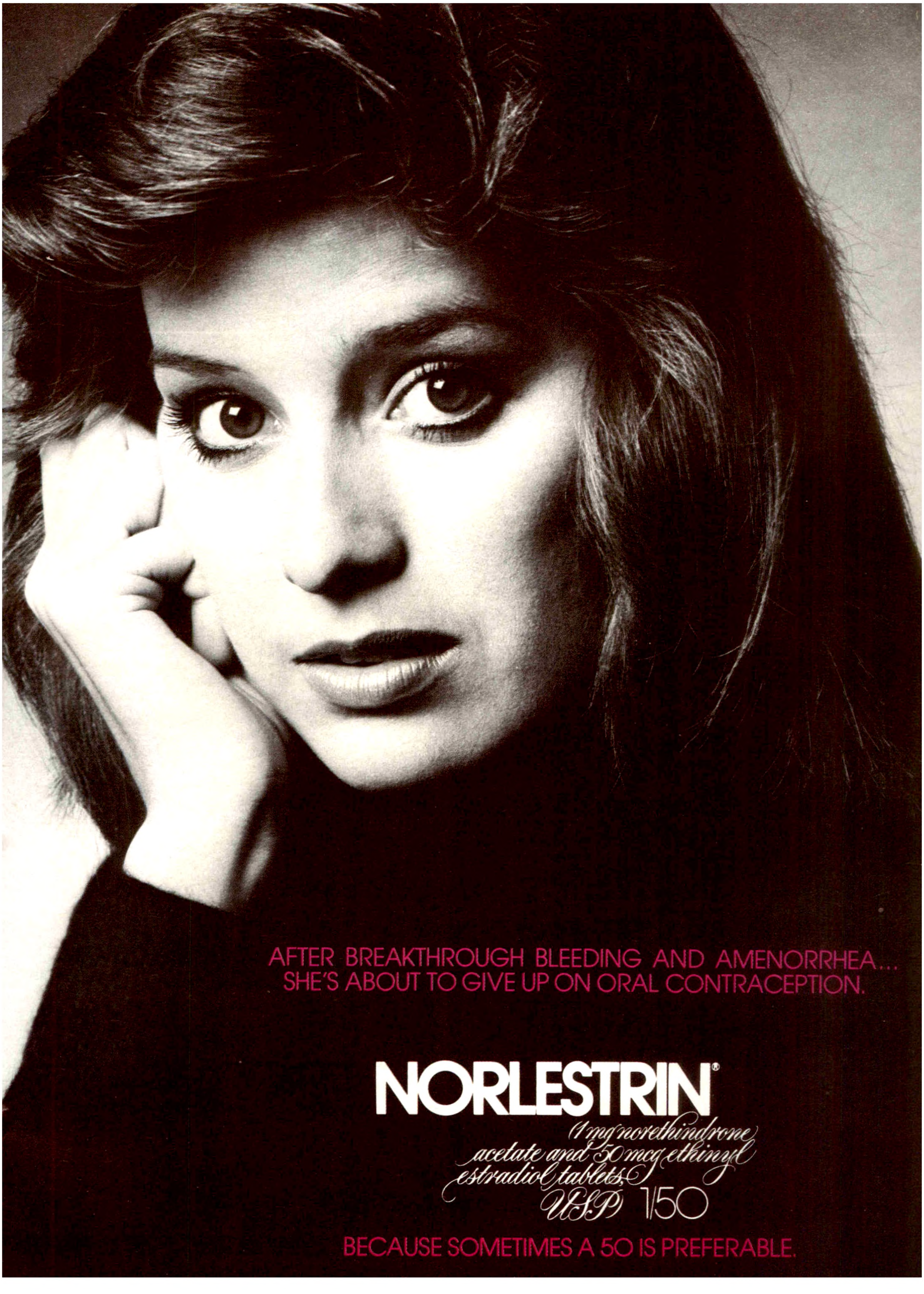
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NORLESTRIN®
(1 mg norethindrone acetate and 50 mcg ethinyl estradiol tablets, USP) 1/50
BECAUSE SOMETIMES A 50 IS PREFERABLE.

Brief Summary of Prescribing Information

NORLESTRIN® (norethindrone acetate and ethinyl estradiol tablets, USP)

See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information. A Brief Summary follows.

DESCRIPTION

Norlestrin Products are progestogen-estrogen combinations.

INDICATIONS AND USAGE

Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0.05 per 100 woman-years; in clinical trials with Norlestrin 2 5/50 involving 96,388 cycles, there was a pregnancy rate of 0.22 per 100 woman-years.

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the isk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS

1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral vascular or coronary artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (See WARNING No. 5)
8. Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1. *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used n oral contraceptives; however, the quantity of estrogen may not be the sole factor involved.

Persistence of Risk: Two studies have suggested that an increased risk may persist for as ong as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction. In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage.

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives ncreases with age after approximately age 30 and, for myocardial infarction, is further ncreased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions.* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopia; papilledema, or retinal vascular lesions.

3. *Carcinoma.* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors.* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring.* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease.* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects.* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure.* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache.* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. *Bleeding Irregularities.* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy.* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-Feeding.* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS

1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.
2. Preexisting uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.
4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.
6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.
7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.
8. Serum folate levels may be depressed.
9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.
10. Certain endocrine and liver function tests and blood components may be affected.

(a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline, and ampicillin.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with oral contraceptives: thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage; hypertension; gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms, breakthrough bleeding; spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature, intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted: premenstrual-like syndrome; cataracts, changes in libido, chorea; changes in appetite; cystitis-like syndrome; headache; nervousness, dizziness; hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum; hemorrhagic eruption, vaginitis, porphyria.

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day after discontinuing medication.

After several months on treatment, bleeding may be reduced to a point of virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED

Norlestrin [21] 1/50 is available in compacts each containing 21 tablets. Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin [21] 2 5/50 is available in compacts each containing 21 tablets. Each tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin [Fe] 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin [FE] 2 5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets. Each pink tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin [28] 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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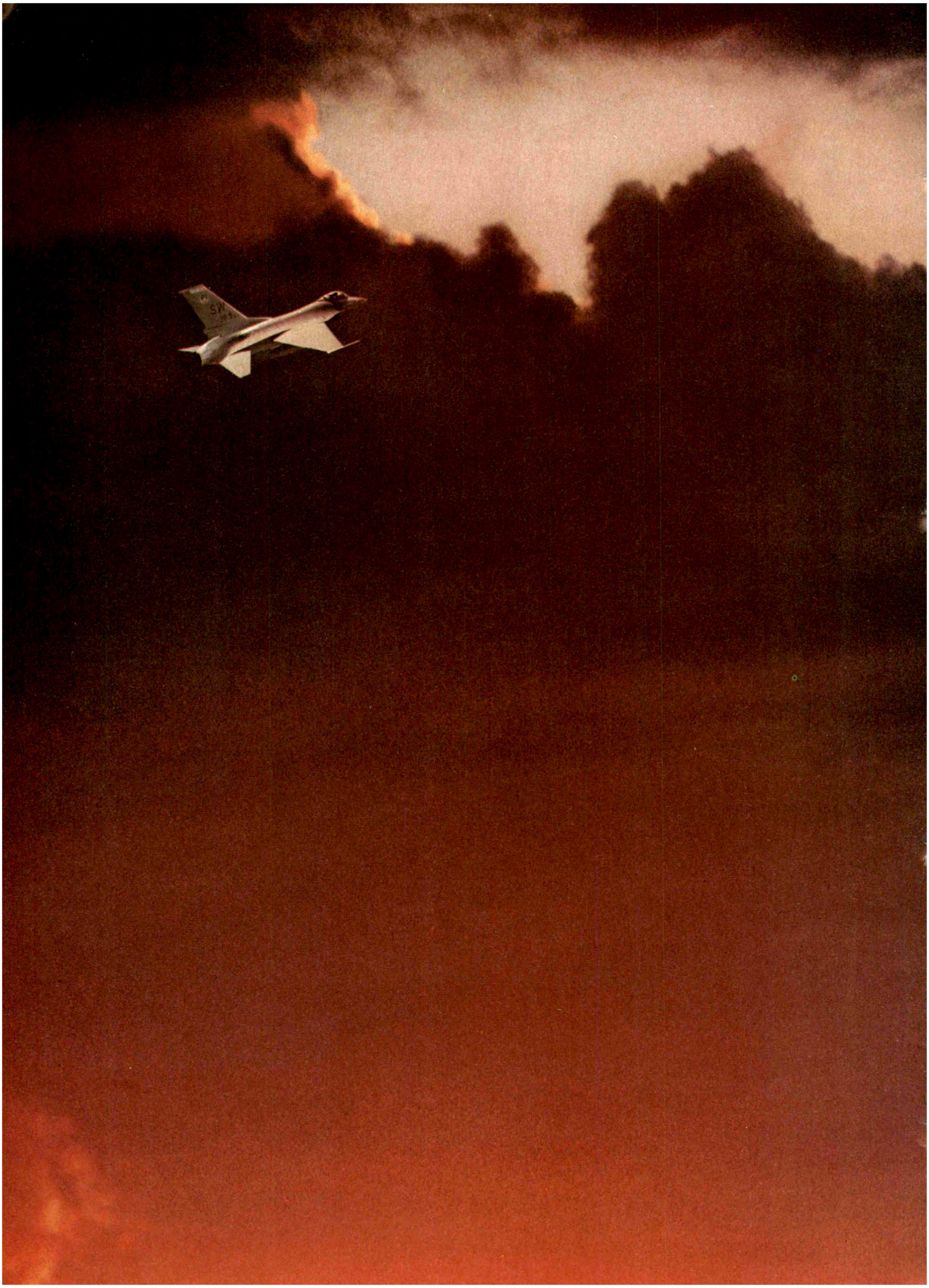
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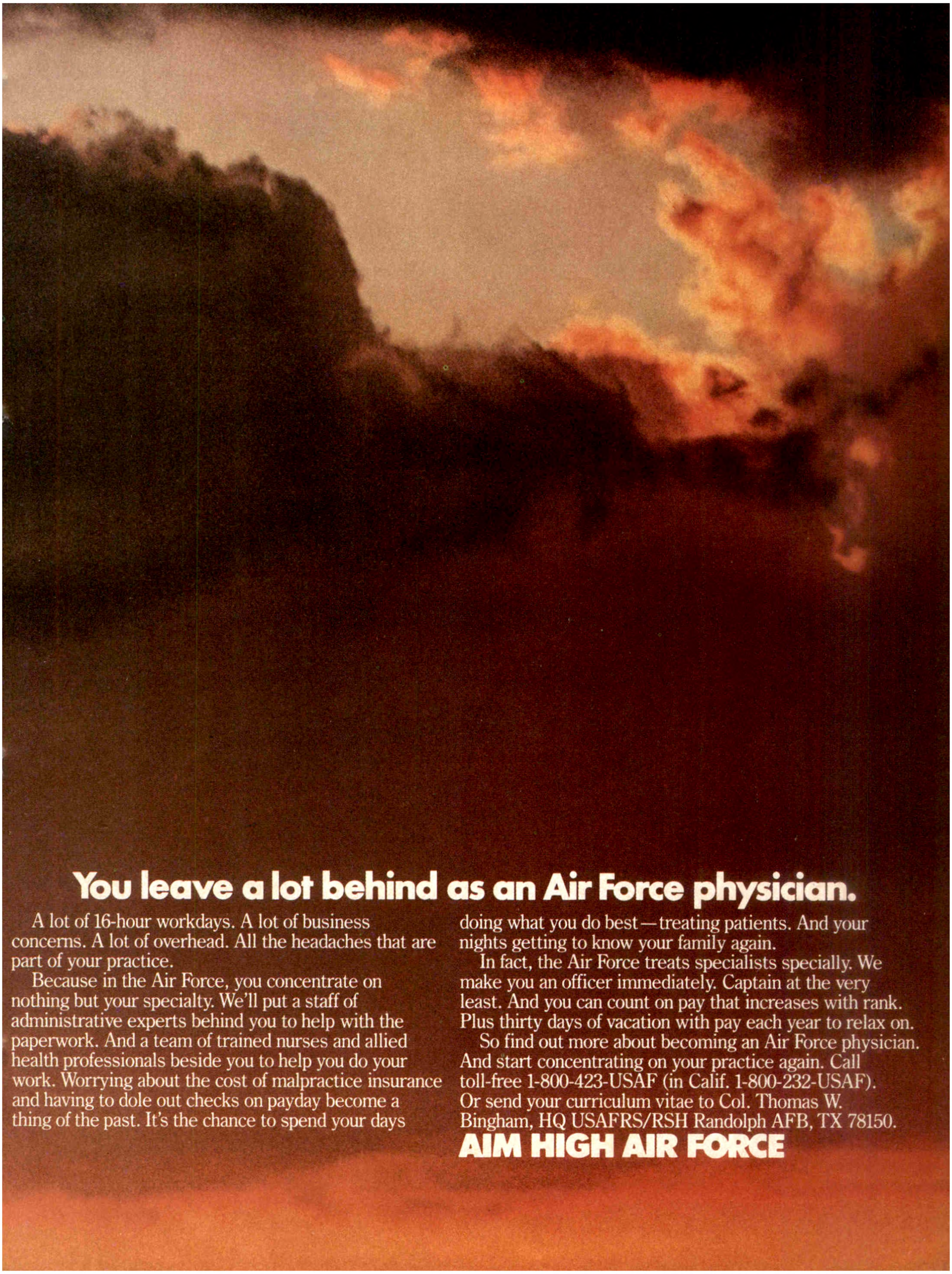

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American Journal of Obstetrics and Gynecology

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INFORMATION FOR AUTHORS

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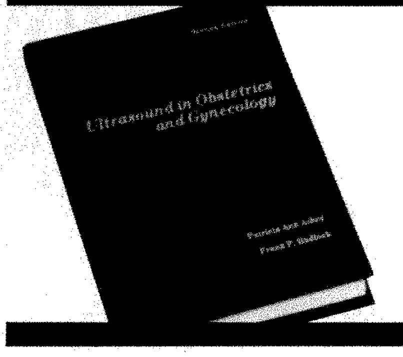

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The first trimester of pregnancy
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Sonographic evaluation of fetal well-being
Multiple gestation
The amniotic fluid and umbilical cord
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Trophoblastic disease
Use of ultrasound in invasive procedures
Introduction to gynecological ultrasound
Sonographic appearance of the normal female pelvis
Vaginal abnormalities
Uterus: abnormalities of size, shape contour and texture
Uterus: abnormalities of the endometrial cavity
Adnexa: non-neoplastic cysts
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Pelvic inflammatory disease
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Ultrasound evaluation of the infertility patient
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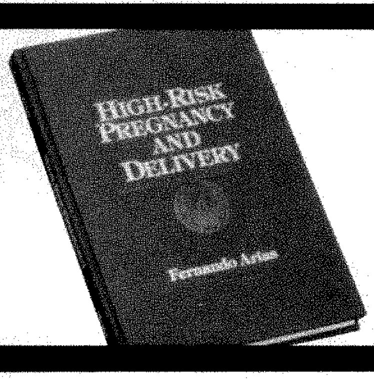

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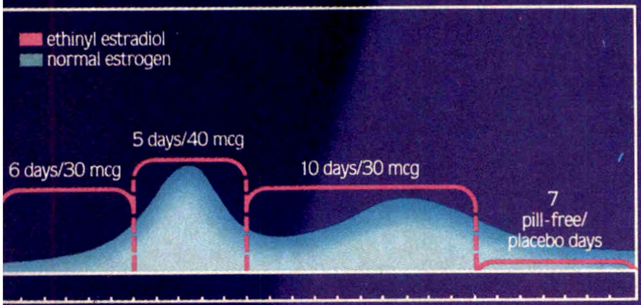

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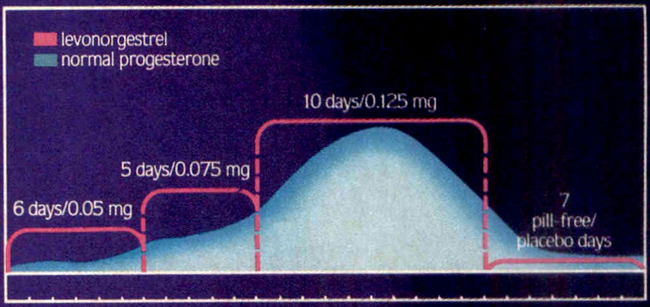

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† Graham H: Letter to Editor. *Br Med J 284*:422, 1982.

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> **Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.**
>
> The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with the use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

PERSISTENCE OF RISK OF VASCULAR DISORDERS—Findings from one study in Britain involving cerebrovascular disease and another in the U.S. concerning MI suggest an increased risk of these conditions in users of OC's persists after discontinuation of the OC's. In the British study, risk of cerebrovascular disease remained elevated in former OC users for at least 6 years after discontinuation. In the U.S. study, increased risk of MI persisted for at least 9 years in women 40 to 49 years old who had used OC's for 5 or more years. Findings in both studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increases in triglycerides and total phospholipids have been observed in patients on OC's. Three studies were performed with Triphasil and no significant alterations in lipid metabolism were noted except for a slight increase in triglyceride levels in 1 study. Clinical significance of these findings remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these preexisting problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination and Pap smear.

2. Under influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's.

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG: free T4 concentration is unaltered.

d. Decreased pregnanediol excretion.

e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings section for information on carcinogenesis.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses. The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration—For maximum contraceptive effectiveness, Triphasil must be taken exactly as directed and at intervals not over 24 hours. (If Triphasil is first taken later than first day of first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on it until after the first 7 consecutive days of use. Possibility of ovulation and conception prior to initiation of medication should be considered.)

Anytime patient misses 1 or 2 brown, white or light-yellow tablets, she should also use another contraceptive method until she has taken a tablet daily for 7 consecutive days.

For full details on dosage and administration see prescribing information in package insert.

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"Is That All There Is?"

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Against a backdrop of marketing threats and increasing legal risks, it is difficult to prepare a presidential address that does not ring with despair and pessimism. "Is that all there is?" Peggy Lee sang in the old days about something missing in life and love. She answered this question with a defiant chorus after each verse of "If that's all there is, my friends, let's keep on dancing. Let's break out the booze and have a ball—if that's all there is."

A close friend of mine, who is now senior minister at the Crystal Cathedral in California, used this title to introduce a series of provocative sermons that carried an answer of eternal hope. My thoughts while contemplating this presentation took on a less ecclesiastical tone, but I do feel a deep concern for the status of our specialty and profession in the year 1984. I love this specialty very much and feel a strong personal commitment to medical service and medical education as a career. Consequently, I am disturbed by the problems that cause good and talented colleagues to leave our profession and direct their interests and energies elsewhere. The attacks against physicians by lawyers, politicians, journalists, and patients have caused the attitude of "medicine isn't any fun anymore" to push out these dedicated physicians and leave many others cynical and discouraged.

Is that all there is? Should we break out the booze and give up? My answer is an emphatic "No." Instead of becoming bitter and bemoaning the loss of the good old days, while destroying ourselves, let us use this as a time for creativity and using our skills more effectively. Remember that people who never change their minds are either perfect or stubborn—we must be flexible!

As one prepares a presidential address, every effort is made to be original, stimulating, and entertaining. After reading at least 20 past presidential addresses, I am inclined to agree with Dr. Warren Pearse,[1] who divided them into three types: (1) a review of the previously written history of an organization or specialty, (2) "the moral uplift" speech urging more "care" into our "cure," and (3) the "obstetrics at the crossroads" lecture with bold new ideas on how to restructure all of us.

The history of our specialty has already been provided in fascinating discussions that range from Greek medicine in Epidaurus to the English obstetric care of Princess Charlotte in 1817. My intention today is to reflect only on the last 3 decades.

The "let's attack American medicine" crusade is an annually recurring theme in our government. Several Central Association presidents have prepared eloquent defenses of the current system of health care in the United States, and others have listed carefully the scientific accomplishments of our specialty during the past 50 years. My concern today does not center on the art or science of our specialty. The quality of both has never been better. My fear is that the pressure on our specialty in 1984 may remove the patient as our primary concern.

We have been advised by past presidential addresses to become superspecialists in some years and to treat the "whole patient" as private-care physicians in other years. Is "obstetrics at the crossroads" in 1984? Probably not. However, we are approaching an intersection of one-way streets marked with road signs of medical marketing, medical malpractice, and medical education. I

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would like to travel each of these three streets today to see if we are on a collision course.

As Casey Stengel, a man who knew a great deal about managing a baseball team, once said, "The past ain't what it used to be." When one recalls a trip or vacation, the pleasant aspects have a way of swimming to the surface while the bad experiences remain submerged. Like last week's pro football highlights, only the good moves are retained in our memories. So it is for some of us "old timers" in medicine. It is not unusual to hear the comment that there is no substitute for the experience life gives you. Likewise it is difficult to resist the temptation to make some interesting observations gleaned from 30 years of personal experience in the fields of general practice, government medicine, clinical obstetrics/gynecology as a resident, solo practitioner, professional corporation partner, and administrative experience as a residency director and medical school professor.

What was it like 30 years ago in the good old days of 1954? Arnie Palmer was only 24 years old and had not won a major golf tournament. Dick Tracy was our favorite comic strip. General Dwight D. Eisenhower was the popular president and he had a clever young attorney by the name of Richard M. Nixon as his vice president. Harold Mack of this city was president of the Central Association of Obstetricians and Gynecologists.

Our office calls in 1954 were $3, house calls were $5, office space rental was under $3 a foot, and an examination table could be purchased for $300. A "byte," however you spelled it, had to do with food, not computer information. The 10-key adding machine was considered the height of sophistication. Not one home had an electronic calculator or a color television set. There was practically no malpractice, although Melvin Belli was already collecting information from medical records in California. There was no medicaid, no medicare, no health maintenance organizations, no preferred provider organizations, no diagnostic related groups, and most patients paid in cash. Seventy-five percent of the physicians in the United States were self-employed, with an average income of $16,000. The location of our practices was selected by personal preference rather than by economic opportunities. These were the good old days, but were they really any better? How about 1984?

Is 1984, as predicted by author George Orwell in 1948, a year in which society is filled with fear and paranoia, consisting of brainwashed citizens who are all under "Big Brother's" control? Is government with the Internal Revenue Service, Food and Drug Administration, and Health and Human Services going to destroy fee-for-service medicine? Will the unlimited classes of graduating lawyers increase the number involved in unbridled, insensitive, inconsiderate, and unethical litigation? Will limited funding of graduate medical education close community hospital residency programs and remove the valuable contribution of our volunteer faculty members? Will our sons and daughters be directed to seek careers outside the medical profession? I personally believe that Orwell's predictions were interesting and perhaps partly correct, but the batteries on his calculator were low when he predicted that people in 1984 had given up.

In 1984 John Naisbitt released his No. 1 best seller *Megatrends*, in which he outlined 10 new directions for transforming our lives. I would enthusiastically recommend that everyone read this book. It is stimulating and informative and offers new insight into our current situation and our likely future. His observations on the development of high tech/high touch during the past 30 years are right on target. To quote Mr. Naisbitt, "Technology and our human potential are the two great challenges and adventures facing humankind today. We must learn to balance the material wonders of technology with the spiritual demands of our human nature. The more high technology we put in our hospitals, the less we want to be born or die there." For example, he explains, life-sustaining equipment has led to the hospice movement, while sophisticated electronic fetal monitoring equipment has encouraged the proliferation of birthing rooms and free-standing birthing centers. His book also introduced the now-popular buzz words in health care of "megabucks" and "megagroups."

Alvin Toffler has written a fascinating book, *The Third Wave*, in which he discusses the drastic changes now taking place in all aspects of our lives. They involve medicine as well as business, industry, politics, economics, and agriculture. There is no question that monumental changes are coming—some tomorrow and some a little later, but come they will.

I personally see 1984 as a year of exciting new changes and challenges. It is a year that has already been characterized by competition. We watched the exciting Twenty-third Summer Olympics in Los Angeles. Our own Detroit Tigers accomplished the impossible by winning 35 of their first 40 major league baseball games, thereby becoming overnight heroes. The Democratic caucuses introduced political blood letting as presidential hopefuls knifed each other in the primaries. For a time the political party conventions became the great American spectator sport and, for sheer brutality, probably rank secondary only to pro football or boxing.

This spirit of competition in 1984 will most certainly carry over into the delivery of health care. Therefore let us take a look at the street labeled "Medical Marketing."

Medical marketing

Dr. Paul Feldstein, University of Michigan health economist, has predicted in one of his "doom and gloom" lectures that the new rules aimed at promoting tougher competition will cause changes in medicine similar to those of the airlines and brokerage houses. The decrease in federal and state dollars will cause at least 1000 of today's 7000 hospitals to close, while the survivors will affiliate and merge to form large conglomerates. The solo practitioners and smaller medical groups will be forced to merge for bargaining power and expanded market capacity.

Dr. Jim Breen, past president of the American College of Obstetricians and Gynecologists, has predicted that the increased competition will result in a decline in physician's income and work hours and in the number of patient visits. He was responsible for the recent publication of the American College of Obstetrics and Gynecology, *Economic Impact*, which clearly explains the changes in health care delivery, financing, and reimbursement as well as the key terms involved.

What has happened during the past 30 years to create the 1984 atmosphere? The government and third parties decided that they could take patients' funds and provide a better medical care system for everyone. They succeeded in building new hospitals and new medical schools and introduced medicaid and medicare with promises to pay for all the medical service needed by all the people. What was the result of these legislative efforts? Health costs have increased more than 250% since 1970.[2] In 1970, 7.2% of the gross national product ($69 billion dollars) was spent on health care compared with 1982 when this figure rose to 10.5% of the gross national product (322 billion dollars). At this rate of growth we would approach more than $1 trillion dollars in the year 1990. It is not surprising that these expenditures for American health care have produced some very strange bedfellows. We see labor bosses and business leaders, Democrats and Republicans, insurance companies and politicians, all united to drive down health care costs. Competition, the byproduct of these current efforts to reduce health care costs, may not be pleasant but it might prevent a totally unacceptable alternative, total government regulation. Also contributing to this competition is the fact that the number of obstetricians and gynecologists has increased 40% in the 1970's (18,876 to 26,305) while the population increased only 11% (208.6 million to 231.7 million).

This combination of physician oversupply and public rebellion at escalating medical costs spells radical changes to come in the way health care is delivered. Many of you are already familiar with the new prospective payment systems such as health maintenance organizations, preferred provider organizations, and independent practice associations. The diagnostic related groups are already in operation as a new system of hospital payments for medicare patients. Hospitals that have been freely allowed to run up the tab, certain of hefty reimbursements, are being forced to keep a very close eye on their expenses. A result of this new system of hospital payments may very well be that many small hospitals, much more oriented to community pride than to the bottom line of profit and loss, will be driven into bankruptcy. Like it or not, the investor-owned facilities that have always had an eye on that bottom line will do much better. They will organize self-care units with minimal care and minimal costs, outpatient satellite clinics, and home health care services. Patients will become locked into certain health plans with very limited referral choices. What does all this mean to you and to me: Is that all there is?

The optimistic side of the coin is that whenever there is change, there is also tremendous opportunity. Physicians must look for new ways to protect their income and take this time to reshape goals and establish priorities. I personally believe that high-quality medical care is cost effective. We can safely decrease the length of stay for our patients. We can decrease the number of unnecessary operations. We can take a closer look at the number of computerized tomographic scans and laboratory tests ordered. As a pilot study at Butterworth Hospital proved in 1977, the cost of open heart surgery was reduced more than $1000.00 per patient when unnecessary procedures were eliminated.[3]

At no time has the push for marketing our product been so strong. Unfortunately, marketing is erroneously equated with advertising and selling. This gap in the physician's knowledge is a major impediment to realization of the benefits that can accrue from the application of marketing principles to medical practice.

In industry it is known that the customer's perceptions are frequently more important than is the actual quality of the product. Likewise, it is difficult for patients to judge physicians purely on their clinical ability. Instead, they respond to the "business aspects" of the practice: the ease of getting an appointment, the physician's bedside manner, the aesthetics of the waiting room, how long the patient has to wait there to see the physician, how pleasant the office staff is, and how much time a physician actually spends with the patient. If a physician does all these things right, he will develop a bigger practice than will an equally skilled physician who neglects the wallpaper in the waiting room, does not have a friendly, reassuring smile, and has no time to spend with the patient listening to her medical, psychological, social, and sexual problems.

As we entered practice in 1954, we were advised to look at the five As of physician qualities: available, adaptable, agreeable, affordable, and able. As we now face the challenges of new marketing strategies in 1984, we should again keep these essential attributes in mind. Physicians must realize that no matter where they went to medical school or how Board certified they are, they are not guaranteed a full waiting room and busy telephone. The physician who implements a marketable program that is patient oriented will realize the goals of growth and high-quality care. The best advertising is still a satisfied patient.

Medical malpractice

One of the major factors in the escalating costs of health care is the legal problem of medical malpractice with megabucks settlements.

Today we practice in a cage of sorts, the bars of which are made from an alloy of legal scrutiny, legal harassment, legal endeavors, some legal expertise, and a good portion of legal omnipotence. No longer can anything less than a perfect result in patient care be considered to be an act of God as it was in 1954.

What happens in 1984 when bad things happen to good people? The patient who has less than an ideal outcome will react with hurt and anger fixed on someone else. The physicians are the logical scapegoats and are an easy prey for the hustling attorney who initiates a lawsuit. Meanwhile, the physicians are convinced that they did their best and had no intention to hurt anyone. The reaction is one of distress and anger. This anger becomes fixed on the patient, the attorney, the courts, the politicians, and the profession and frequently results in the physician becoming cynical and bitter.

What happens to the settlement dollar? As many of us know, in professional liability suits only the lawyers win. The patient and the physicians are the losers. Of each dollar awarded, the unfortunate patient collects a total of 18¢, the attorneys 40¢, and the legal court costs take up the remaining 42¢.[4] The physician and the insurance company pay the entire dollar.

The magnitude of the problem can be appreciated when one looks at the reports of recent surveys. In Michigan one out of four physicians have been sued for malpractice and last year's professional liability premiums increased an average of 16.8%. Awards are increasing at an average of 20% a year. The incidence of lawsuits directed toward obstetricians in Florida has been reported to be as high as one out of three, and premium rates have gone as high as $50,000 a year.

In 1983 the American College of Obstetricians/Gynecologists conducted a survey of some 4000 Fellows and found that more than 60% had been sued at least once and that across the nation 20% had been sued three or more times. As a result of this threat, studies show that more than a quarter of physicians will abandon obstetrics in the near future. Is that all there is? Should we give up and quit? Is there anything else that we can do?

First of all, let us drop the word "malpractice," which literally means bad practice, and use the words "professional liability." We must make every attempt to substitute the term "neurologically deficient" in place of "brain-damaged child," which generates those megabucks settlements from misinformed juries. Birth trauma is not always the cause. In fact, events may occur at conception or during intrauterine life without a chance of being diagnosed or prevented by any physician.

In the new book *Obstetrics, Gynecology and the Law,* the authors present the following conclusion: "Most cases could have been prevented if the health care providers had exercised greater vigilance, diligence, and attention to details of patient care, particularly in communicating with the patient." They conclude that prophylaxis can beat malpractice. My personal experience in reviewing many lengthy hospital charts and office records for local attorneys has convinced me that there are areas in which obstetricians and gynecologists can protect themselves more effectively.

Although it may be appropriate to consider every patient as a potential plaintiff, that fear should not be allowed to interfere with the doctor-patient relationship. The physician should personally counsel the patient and obtain the informed consent. The use of tapes and written descriptions will aid in assuring a complete coverage of the diagnosis, treatment, and prognosis. The greater the risk of the procedure, the more detailed the explanation should be to the patient.

Each of us should be aware of our own limitations and carefully consider whether the elective surgery we schedule is really necessary. Is our training and experience adequate to perform the once-a-year operations or would consultation be beneficial to the patient? Have we allowed enough time in our busy schedules for difficult labors or operative surprises to avoid hurrying and increasing the risks?

Finally, we must assume our responsibility to evaluate colleagues who provide borderline treatment. The education of these physicians and the care of "sick" doctors may be one of the most important challenges of this problem.

Lines of communication must be improved between doctors and partners, doctors and house staff, and doctors and patients. Documentation of findings, decisions, treatment, and results must be included in the records. A physician should do his own charting and do it well. This will not only aid in legal defense but also contribute significantly to better patient care.

Do not be reluctant to speak to attorneys—not all are out to get you. Many of you will be invited to give testimony or depositions under oath. Your defense attorney may be the only one to save you when you are adrift on the legal sea without a paddle.

Finally, we must convince the public that there is something terribly unfair about 500,000 physicians paying premiums for 200,000,000 people. Professional liability is a significant and expensive national problem.

Getting professional liability out of the court system will require legislative reforms. Getting these changes through a lawyer-dominated legislature will not be easy. We must learn to use the political system to our advantage. We must reduce the number of law suits without merit that go to court. We must limit the awards for noneconomic losses such as pain or loss of affection. We must change the contigency fee schedule of attorneys.

Several states have already introduced legislation to bring about the above changes. In Michigan a recent bill introduced in the Michigan senate has criteria for the control of financial rewards paid to the expert witnesses. This would limit each one to a total of 10 cases, and require the expert witness to be licensed in the state and spend at least 75% of his or her time in the teaching or practice of the specialty of obstetrics and gynecology. The "hired guns" who travel first class on superjets instead of stagecoaches might be forced to leave this lucrative subspecialty.

Although the future seems ominous, we must continue to maintain our dignity, compassion, and empathy with patients. Although the lawyers far outnumber us, they cannot match us in intelligence, integrity, industry, and dedication. With the help of our patients, this specialty shall prevail, and the patient will ultimately be the winner.

Medical education

My final concern today is of a more personal nature than that of medical marketing and medical liability. Each physician, as a talented, privileged, and highly educated person, has an obligation. This may take the form of teaching, research, administrative responsibilities, community leadership, or filling financial needs. Each physician must pick his or her own way to fulfill this obligation. Failure to accept this responsibility results in a lack of self-fulfillment, and one quickly becomes confined in "little prisons" of self-concern.

There is no such thing as a free ride. The physicians who just tend to their practices are not doing their share. Eventually we all have to give something back if we want our profession, medical schools, and communities to survive. We must take time to become involved in expanding our images as persons who care—in or out of the office. Teaching is the best learning experience and is as essential as attending another postgraduate course to maintain one's competence. One of my lifetime goals has been to influence, in a positive way, the education of residents and students in our specialty. One source of great personal satisfaction and pride has been to serve as a community hospital residency director for almost 20 years. We have witnessed the changing trends in medical education from the Health Manpower Act of 1968, providing generous funding for increased medical school enrollments, to the Graduate Medical Education National Advisory Committee report limiting funds and projecting an excess of 70,000 physicians by 1990. The increased cost of medical tuition and expenses has caused 83% of our recent graduates to have debts averaging more than $21,000, with some as high as $80,000, according to a 1983 survey by the Association of American Medical Colleges. Although house staff salaries have increased during recent years, monthly paychecks still generate the same question from residents and their spouses with "Is that all there is?"

Our future hopes rest with the young students and residents we are now training. Are they really prepared for real-life medicine? How about ethics in today's tough decisions? How about cost containment? How about teaching methods to cope adequately with the stresses of a busy obstetric practice? Have we included an adequate exposure to prevention as well as treatment of disease? Are we teaching them to do things for themselves? An old Chinese proverb might speak to continuing self-education when it says, "If you give a man a fish, you feed him for the day, but if you teach him how to fish, you feed him for life."

Although I admit my bias, I feel that the input of the teaching hospital and the volunteer faculty is vital to graduate medical education. They also make a significant contribution to the clinical training of medical students and continuing medical education for practicing physicians. All of us who are involved in community hospital teaching programs are aware that the third-party reimbursement system is no longer a guarantee. We are aware that education programs do generate administrative, personnel, payroll, library, and research costs. The space used for offices, housing, and sleep does not generate revenue.

My personal fear is that education, unfortunately, may be one of the first items to be slashed when costs become a major concern in a hospital budget. Although several alternative methods of funding for graduate medical education are beginning to surface, I would solicit the support of each one of you to preserve this valuable aspect of our educational system. The Central Asociation of Obstetricians and Gynecologists has always fostered education, and many of our members have dedicated themselves to developing new teaching materials, curriculum designs, and national guidelines for resident evaluations. Many of us were delighted in 1983 when the Council for Resident Education in Obstetrics and Gynecology added a community hospital program director to its membership. It is hoped that we will not allow the cost-containment efforts to threaten the future of graduate education in our specialty and, as a result, threaten the quality of health care available in the future.

Carl Menninger once said that "attitude is more important than facts." Likewise, how you feel as a physician and teacher is as important as what you know when you serve as a role model for residents and students. It has been said that one half of all we teach medical students is obsolete or wrong in a decade. My problem has been that I have never been able to figure out which half. We must remember that clinical problems have many dimensions. Solving them well takes time and practice, but then so does solving them badly. Teaching the difference is what medicine is all about.

I am convinced that the current medical education programs in obstetrics and gynecology do rank with the best in the world, and we do not have to apologize for our efforts in this area. However, we must be prepared to accept the challenge of Mr. Naisbitt in applying high technology in a high-touch manner. We must reemphasize the spirit of humanity and concern for people that is implicitly necessary for the complete practice of our specialty. We must remember that empathy is not a substitute for knowledge, but neither can sophisticated clinical skills replace our ethical standards. Laboratory findings are no more essential than is concern for the patient's family. Subspecialization is not the entire answer to good patient care and residency education. We must not allow it to fragment our specialty and squeeze the general obstetrician-gynecologists out of our hospitals and away from their patients.

At the feast of life there are always a few freeloaders. They are takers, not givers. They refuse to teach, ignore errant colleagues, ignore social, economic, and political challenges, and ignore obligations to professional organizations. It is a fact that only one half of all licensed physicians in the United States belong to the American Medical Association. The reasons are that it costs too much or they do not approve of American Medical Association actions. In reality, these nonmembers derive the exact same benefits of the American Medical Association without paying dues. Why pay the streetcar conductor if you can hang on for free?

Nicholas Butler, former president of Columbia University, described three kinds of people in the world: those who do not know what is happening, those who watch what is happening, and those who make things happen. I would urge all of you to get involved, be informed, and make things happen.

In summary, each of us has a unique opportunity to win support for our team in the 1984 competition. People do respect their physicians and their opinions. It is time to stop feeling sorry for ourselves and looking for someone to blame. We can develop a successful marketing plan that is sensitive to the patient's needs and desires. We can use our tremendous clout as individuals and organizations to change the legal attacks. We must pass something worthwhile on to the next generation.

I cannot help but recall the honor and surprise I experienced two years ago when I was chosen to be your President-Elect. Two distinguished Past Presidents and dear friends were among the first to offer their congratulations and to offer to escort me down that center aisle today. Within two months of that day, both of them had died unexpectedly.

I would like to close with a paraphrasing of their presidential addresses, which also answer my question, "Is that all there is?"

Ten years ago, Dr. Russell J. Paalman[5] challenged us with "Let the members of the Central Association strive for the abundant life for women. If we pursue these goals, we will be rewarded with an abundant life for ourselves."

Dr. Thomas W. McElin[6] concluded his eloquent address in 1971 with "If you work in a profession, then in heaven's name, work for it. If you live by a profession, live for it. Help your co-workers to respect the great power that protects you. Speak well for it, stand for it."

I urge you not to give up but to work harder to change that which is not the best for our patients, our students, and ourselves.

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Vaginal breech delivery of selected infants weighing more than 2000 grams

A retrospective analysis of seven years' experience

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This retrospective study analyzes 580 term and near-term singleton pregnancies complicated by breech presentation from 1976 through 1982. Vaginal delivery was achieved in 174 patients (30%), 135 of which were selectively allowed a trial of labor. Six infant deaths occurred (1%); all were neonatal deaths directly related to lethal congenital anomalies, for a corrected neonatal mortality rate of 0%. No significant difference was found in the incidence of low Apgar scores, traumatic birth injury, or requirement for neonatal resuscitation between those infants delivered by cesarean section and those delivered vaginally. Although no maternal deaths occurred, cesarean section was associated with a 38-fold increase in significant maternal morbidity. These data suggest that with careful patient selection and fetal monitoring, vaginal delivery of the term or near-term breech infant remains a real alternative to routine cesarean delivery of all breech infants. A selection and management protocol is proposed. (AM J OBSTET GYNECOL 1985;152:145-55.)

Key words: Vaginal breech delivery, breech presentation, perinatal morbidity and mortality

Intrapartum management of the near-term pregnancy complicated by breech presentation remains a controversial issue in contemporary obstetrics. Vaginal delivery of breech infants has been reported to be associated with increased perinatal morbidity and mortality rates when compared with either cesarean breech delivery or vaginal delivery of those infants presenting in cephalic position.[1] With the improvement of perioperative support care, the previously significant maternal risk associated with cesarean section has been reduced. Cesarean section has been advocated for all viable breech infants of 35 weeks' gestational age or greater in an attempt to reduce the incidence of traumatic birth injuries and intrapartum asphyxia associated with vaginal breech delivery.[2] To accept this approach, one must justify the increased maternal surgical morbidity by showing a consistent improvement in perinatal outcome. Achievement of maximum safety for both mother and infant is the primary goal in any plan for delivery.

This retrospective study was undertaken to evaluate the maternal and infant outcome of selected vaginal delivery of term and near-term breech infants when compared with breech delivery by cesarean section at The University of Alabama Hospital complex in Birmingham from January, 1976, through December, 1982. During this period a generally accepted policy was in effect to allow a trial of labor and vaginal delivery for selected patients at or near term with infants in the breech presentation.

Material and methods

This retrospective analysis consists of 580 gravid women with singleton gestations and breech presentations with fetal cardiac activity who were admitted to The University of Alabama Hospital complex in Birmingham from 1976 through 1982. The gestational age was 34 weeks or greater and the birth weight approximately 2000 gm or more. Those women treated by cesarean section for the primary indication of "premature breech" at a gestational age of 34 weeks or less were excluded. Infants less than 34 weeks' gestational age were excluded from this study because their management and types of neonatal complications were intrinsically different from those directly related to the events of labor and delivery for the more mature infant. The two obstetric units involved were supervised by the obstetric faculty and resident staff of the University.

A small number of patients in an advanced stage of labor required immediate delivery on admission to the hospital. The remaining patients were evaluated clin-

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Table I. Breech configuration and mode of delivery

Breech configuration		*Vaginal delivery (No.)*	*Cesarean section (no.)*	*Total*
Type	*%*			
Frank	55	129	188	317
Complete	14	26	54	80
Incomplete	30	19	154	173
Unknown	1.7	0	10	10
Frank and complete	68	155 (39%)	242 (61%)	397 (100%)
Total		174 (30%)	406 (70%)	580 (100%)

Table II. Mode of delivery: Planned versus immediate

Type of delivery	*Planned (No.)*	*Immediate (No.)*	*Total (No.)*
Cesarean section	367	39	406
Vaginal	135	39*	174
Total	502	78	580

*Of all breech infants, 6.7% required immediate vaginal delivery on admission.

ically to determine their candidacy for a trial of labor. Although no written protocol concerning the management of the near-term breech was in effect, a set of general minimal criteria was used to select patients for a trial of labor that would possibly lead to vaginal delivery. These criteria included: gestational age of at least 34 weeks; estimated fetal weight between 2000 and 3800 gm; in general, breech presentations in frank or complete configuration; maternal x-ray pelvimetry demonstrating no contracted dimensions; flexion of the fetal head; and the absence of detectable congenital anomalies. One standard used for minimum pelvic dimensions was that proposed by Collea et al.[3] Early in the study several participants with babies presenting in the incomplete breech position were allowed to labor.

Continuous external or internal electronic fetal monitoring was used in all patients permitted to labor after clinical evaluation. Oxytocin was used intravenously in selected patients to augment dysfunctional labor. All deliveries were conducted under the direct supervision of a staff physician or chief resident. Assisted breech extractions were conducted for all vaginal deliveries except six, who were subjected to total extractions. Resident pediatric staff were present at delivery for immediate neonatal resuscitation when necessary. Surgical anesthesia and cesarean section capability were immediately available.

The data for analysis were obtained from review of maternal and neonatal medical records including prenatal, intrapartum, and postpartum courses and neonatal outcome with selected pediatric follow-up for certain infants. All medical records were reviewed by R. K. T.

Results

Between 1976 and 1982, 580 mother-infant pairs were available for study. The average maternal age was 23.7 years (range 13 to 46 years). Fifty-seven percent of the patients were black and 43% were white. Primiparous women composed 48% of the population; 8.0% of the multiparous women had a history of previous breech presentations. No statistical difference was evident in maternal characteristics of age and race between patients delivered by cesarean section and those delivered vaginally. Vaginal delivery was achieved in 37% of multiparous patients while primiparous women were delivered vaginally in 22% of cases, representing a significant statistical difference. However, careful review of the documented indications for cesarean section in primiparous patients revealed that 85% of these procedures had at least one primary indication including inadequate x-ray pelvimetry, incomplete breech presentation, fetal macrosomia, failure to progress, or fetal distress. Other miscellaneous indications accounted for an additional 10%, none of which were related to maternal parity. Primiparity was used as the singular indication for cesarean section in only six patients (2.8%).

Frank breech presentation was the most frequently encountered configuration (Table I). With the exception of seven infants who were delivered early in the period of study, patients with incomplete breech presentations were excluded from a trial of labor secondary to an increased risk of cord prolapse and possibly fetal injury. The remaining group of infants in the frank and complete breech positions composed 68% of the study population and were considered candidates for a trial of labor and possible vaginal delivery. Considering the entire range of birth weights, the estimated fetal weight was within 600 gm of the actual birth weight in 69% of cases; greater accuracy was found between 2500 and 4000 gm, where 82% of estimates were within 600 gm of the actual weight.

X-ray pelvimetry was used to determine the size and

Table III. Infant morbidity by mode of delivery*

		5 min Apgar score <7				*Major birth injury*			
Mode of delivery	*No. of patients*	*No.*	*%*	*Relative risk*	*p Value*	*No.*	*%*	*Relative risk*	*p Value*
Cesarean section	402	3	0.75	1.0	NS†	2	0.50	1.0	NS†
Planned vaginal	134	2	1.49	2.0		2	1.49	3.0	
Immediate vaginal	38	3	7.89	10.5	0.0003‡	1	2.63	5.3	NS‡

*Six infants with lethal congenital malformations are excluded.

†p Value compares cesarean section with planned vaginal delivery.

‡p Value compares cesarean section with immediate vaginal delivery.

configuration of the maternal pelvis in 334 patients (58%) considered for vaginal delivery; 57.5% of these determinations were considered "adequate" by a variety of standards. Hyperextension of the fetal head was identified in 23 of the 334 patients evaluated by abdominal x-ray films (7%); these were excluded from a trial of labor.

Vaginal delivery was accomplished in 174 patients (30.0%) while the remaining 406 were delivered by cesarean section (Table I). Forty-one percent of all frank breech infants were delivered vaginally.

Seventy-eight patients (13.4%) required immediate vaginal or cesarean delivery on admission, most commonly related to advanced stages of labor. Thirty-nine infants in this situation were delivered vaginally, 6.7% of all pregnancies studied. The remaining 502 patients received further evaluation before planned delivery (Table II).

Of the patients selected for a trial of labor, 36 received intravenous oxytocin for augmentation of dysfunctional labor. Continuous internal electronic fetal monitoring was used when labor was augmented. Vaginal delivery was achieved in 28 of these 36 patients (78%). None of the 28 infants delivered vaginally had 5-minute Apgar scores <7 or delivery trauma. The remaining eight patients were delivered by cesarean section because of failure to progress in labor; no cesarean sections were performed for fetal distress in this group, and none of these infants developed neonatal complications. Twenty-one percent of patients with planned vaginal delivery required oxytocin augmentation of labor.

Except for six total breech extractions, all of the vaginal deliveries were performed by assisted breech extraction after spontaneous delivery to the umbilicus. Piper forceps were applied to the after-coming fetal head in 40% of the cases. Pudendal or local anesthesia was used for 84% of vaginal deliveries. Vaginal delivery was complicated by a 29% incidence of third- and fourth-degree perineal lacerations.

Indications for cesarean section included incomplete breech presentation, inadequate maternal pelvimetry, fetal macrosomia, and failure to progress. Fetal distress was the primary indication for surgery in only 5.4% of cesarean sections. General anesthesia was the only method of major surgical anesthesia available in one of the obstetric units and was used in 87% of all cesarean sections.

Fifty-two percent of the infants delivered were female. No infant had hyaline membrane disease or respiratory distress syndrome. Congenital malformations were identified in 41 of the 580 infants (7.1%); 16 (2.8%) were described as major anomalies. No intrapartum deaths occurred when fetal heart tones were present on admission. Six infants died neonatally (1%). All these infants had severe, congenital malformations incompatible with life. The overall neonatal mortality rate was 10.3/1000 live births. With the exclusion of these six infants, the corrected neonatal mortality rate was 0%.

Prolapse of the umbilical cord occurred only once (0.17%). This patient presented with an incomplete breech that was crowning on admission with an obvious cord prolapse. The infant was delivered by emergency total breech extraction without traumatic injury. Apgar scores were 7 and 9 at 1 and 5 minutes, respectively; the infant had no neonatal complications.

Excluding the six infants with lethal congenital anomalies, 30% of the infants had Apgar scores <7 at 1 minute. However, at 5 minutes only eight infants received Apgar scores <7 (Table III). Although the relative risk appears to be 2:1, there was no statistical difference in the incidence of low 5-minute Apgar scores in infants delivered by cesarean section and those with planned vaginal delivery. However, with immediate vaginal delivery the relative risk of a low 5-minute Apgar score was 10.5 when compared with that of cesarean section. In the group of primiparous patients delivered vaginally, only one low 5-minute Apgar score was found, and this was an emergency vaginal delivery. The remaining four were found in multiparous patients.

Table IV. Maternal complications related to method of delivery

Maternal complication	*Cesarean section*		*Vaginal delivery*		*Relative Risk*
	No.	*%*	*No.*	*%*	
Total	406		174		
Endoparametritis	125	31	1	0.57	54
Transfusion	36	8.9	2	1.1	8
Wound complication	18	4.4		—	
Blood culture positive	10	2.5		—	
Major anesthetic complications	4	1.0		—	
Overall complication rate*		42		1.1	38
Hospital stay after delivery (days)	5.9		3.2		p = 0.0001

*Percentage of patients per delivery group who experienced major morbidity after delivery.

Several fetal injuries were identified during this study. Lacerations of the buttocks at cesarean section and less frequently from application of fetal scalp electrode placement made up the largest group of minor injuries. Damage to the brachial plexus was the most common major injury. Of 134 patients allowed a trial of labor that progressed to vaginal delivery, two infants sustained injuries to the brachial plexus, neither with augmentation of labor, and both were in multiparous gravid women (Table III). The first was a 3250 gm frank breech infant delivered with adequate x-ray pelvimetry. The delivery was complicated by bilateral nuchal arms. The infant acquired bilateral brachial plexus injuries, which resolved completely by 1 year of age. The second infant weighed 3460 gm and presented in 1976 as an incomplete breech presentation with adequate maternal pelvimetry. The infant sustained a left brachial plexus injury, which completely resolved by 6 months of age. In the group of infants delivered by cesarean section, two injuries also occurred. One infant was a 2680 gm frank breech presentation delivered by repeat low transverse cesarean section when the mother was in labor. The baby sustained a unilateral brachial plexus injury, which resolved during the postnatal hospitalization. The second injury, a spiral fracture of the left femur, occurred during a low transverse cesarean section performed for a 2720 gm incomplete breech presentation when the mother was in labor with inadequate x-ray pelvimetry. There was no statistically significant difference in the incidence of major birth injury between planned vaginal delivery and cesarean section. The only injury to occur during emergency vaginal delivery was a clavicular fracture in a 2800 gm frank breech infant delivered by a primiparous mother who was crowning on admission. This was the only birth trauma to occur in a primiparous patient delivered vaginally.

Another measure of perinatal asphyxia is the requirement for immediate neonatal resuscitation. Pediatric resuscitation was required in 45% to 49% of all groups of deliveries whether cesarean section or vaginal delivery, with no statistical difference. The percentages of infants requiring admission to the intensive care unit were statistically the same, 34% and 32%, representing the vaginal delivery group and cesarean section group, respectively. The average duration of stay in the intensive care unit per infant was 3.9 days, with no difference between groups. Approximately one third of all infants from both the vaginal and cesarean section delivery groups admitted for intensive care remained less than 24 hours, primarily for observation without identifiable complications.

There were no maternal deaths; however, significant maternal morbidity did occur with cesarean section. Abdominal delivery was associated with a 42% incidence of significant maternal complications while, excluding episiotomies, maternal complications occurred in 1.1% of vaginal deliveries (Table IV). This represents a 38-fold increased relative risk of major maternal morbidity. Post–cesarean section endoparametritis was the most frequent complication and occurred in 31% of all cesarean deliveries. Major complications of anesthesia occurred in four patients (1.0%) treated by cesarean section. One patient had a total fascial evisceration. Eighty-one patients who underwent cesarean section (20%) remained hospitalized for 7 or more days; two required prolonged hospitalization. One had severe endoparametritis with a pelvic abscess that required total abdominal hysterectomy. The other patient, with known Crohn's disease, had bowel complications during cesarean section and required multiple surgical procedures.

Comment

The increase in perinatal morbidity and mortality rates associated with breech presentation and vaginal delivery can be related to multiple factors: (1) an increased incidence of prematurity and its complications; (2) severe, lethal congenital anomalies; (3) intrapartum asphyxia from uteroplacental insufficiency, prolonged difficult labor, cord compression with contractions, prolapse of the umbilical cord, or difficult vaginal delivery; and (4) traumatic birth injury.

The incidence of congenital malformations associated with breech presentation near term is about 5%, a twofold to threefold increase over their vertex counterparts (2.1%).[3] Kauppila[4] reported a 0.8% to 1.0% incidence of lethal congenital malformations at term, similar to the incidence found in the present study. The vast majority of severe congenital anomalies are not detected before delivery; routine cesarean section would not eliminate neonatal mortality related to these anomalies.

The intrapartum development of fetal asphyxia continues to be a major, potentially preventable, cause of perinatal morbidity and mortality for the near-term breech infant. Prolapse of the umbilical cord and prolonged, difficult vaginal delivery are two primary causes of fetal asphyxia and acidosis. The incidence of prolapse of the umbilical cord for breech presentations overall is reported to be between 1.4% and 6%.[1, 5-8] In vertex presentations this complication occurs in about 0.5% of cases, which is similar to the average incidence in frank breech presentations of 0.4%.[6, 7] Complete breech presentation is associated with a 4% to 5% incidence of cord prolapse; this risk may approach as much as 15% in the incomplete breech presentation.[7] The high perinatal mortality rate associated with cord prolapse may be related to delay in the recognition of occult cord compression with the subsequent development of severe, prolonged asphyxia. To avoid this unpredictable complication, Piper and Bachman[9] recommended immediate total breech extraction with complete dilatation of the cervix. Routine cesarean section of all viable, breech infants 35 weeks gestation or more was proposed by Wright[2] to prevent perinatal mortality caused by cord prolapse and compression during the second stage of labor. Continuous electronic fetal monitoring allows early identification of uteroplacental insufficiency as well as acute fetal distress and provides an opportunity for immediate intervention by cesarean section or, more rarely, use of total breech extraction if delivery is imminent.

Apgar scores at 1 and 5 minutes are valuable measures of the degree of intrapartum and postpartum infant asphyxia and the need for aggressive neonatal resuscitation. Mann and Gallant[10] reported a retrospective study of 457 breech deliveries with a 36% incidence of 1-minute Apgar scores <7 and a 9.6% incidence of 5-minute Apgar scores <7, with no difference between scores with either cesarean section or vaginal delivery. In the present study no statistical difference was found between the two nonemergent delivery methods in neonatal parameters related to asphyxia. In 1982 Green et al.[11] showed no significant improvement in the rate of birth asphyxia, with an increase in cesarean section rate for term breech deliveries from 22% to 94%.

Expertise in the intrapartum evaluation, judgment, management, and particularly technical skills required for vaginal breech delivery can significantly reduce the risk of severe neonatal asphyxia and trauma for an infant delivered by the vaginal route.[6, 8, 12] Gimovsky et al.[12] emphasize the importance of residency training to equip practitioners with the expertise necessary for management of precipitate vaginal breech delivery at term (11.4% in that study). In the present study 38 infants (6.6%) without lethal anomalies required immediate vaginal breech delivery on admission. It is this very group of infants, who have an 8½-fold increased risk of asphyxia, in whom the experience and skill of the obstetrician in the maneuvers required for vaginal breech delivery learned during residency training are critical to achieve safer vaginal delivery and to minimize the risk of additional birth asphyxia and trauma.

Traumatic birth injury contributes significantly to the increased perinatal morbidity and mortality rates related to vaginal breech delivery. The most dangerous traumatic injuries related to breech delivery include intracranial hemorrhage, transection of the cervical spinal cord, and injuries to the brachial plexus or intraabdominal organs. Hyperextension of the fetal head in utero is associated with a 21% incidence of cervical cord transection if delivery is effected vaginally; this complication is avoidable by careful cesarean delivery.[13] This situation can be identified by x-ray of the maternal abdomen; the attitude of the fetal head should be evaluated in any patient being considered for a trial of labor. Brachial plexus injury is most frequently seen in deliveries complicated by nuchal arms and entrapment of the after-coming fetal head, which are also associated with cord compression and fetal asphyxia. Brachial plexus injury was reported in 8.5% of term, vaginal breech deliveries by Fischer-Rasmussen and Trolle[1] in 1967. The shoulder traction of the Mauriceau-Smellie-Veit maneuver has been associated with an increased incidence of severe brachial plexus injuries.[14] Piper forceps may assist in the proper flexion delivery of the after-coming fetal head.[9, 14] Tan[14] reported approximately 69% resolution of brachial plexus injuries within 3 months after delivery.

Rovinsky et al.[8] relate the incidence of traumatic morbidity and mortality to three factors: ". . . maternal pelvic capacity, size of the fetus, and manipulation employed to effect delivery." Similarly Moore and Steptoe[7] correlate increasing complexity and difficulty of vaginal delivery with an increased neonatal mortality rate. The assisted breech extraction with spontaneous delivery to

Table V. Proposed protocol for breech trial of labor and vaginal delivery

Selection	*Management*
Frank or complete breech	Prerequisites
Fetal weight 2000-3600 gm	Immediate cesarean section capability
Gestational age ≥34 wk	Anesthesia support
Normal x-ray pelvimetry*	Pediatric support
Flexed fetal head	Obstetrician skilled in vaginal breech delivery
Possible sonar evaluation	Labor
Biparietal diameter and estimated fetal weight	Spontaneous, Friedman curve
Congenital malformations	Continuous electronic fetal monitoring
Neuromuscular function	Oxytocin for dysfunctional labor, if necessary, after careful evaluation
No other maternal or fetal indications for abdominal delivery	Delivery
	Generous episiotomy
	Spontaneous delivery to umbilicus; assisted breech extraction
	Piper forceps to after-coming fetal head, with any delay in delivery
	Cesarean section for fetal distress or failure to progress in labor with adequate contractions

*X-ray pelvimetry—minimum normal measurements[6]:

1. Inlet
    Transverse 12.0 cm
    Anterior/posterior 11.0 cm
2. Midpelvis
    Bispinous 10.0 cm
3. Sacrum
    Hollow, no significant anterior inclination
4. Subpubic arch
    Not narrowed

the umbilicus has become the method of choice for vaginal breech delivery; total breech extraction is reserved for rare emergency situations. Cesarean section as a method of delivery must be approached with the same care and expertise as a vaginal delivery if atraumatic birth is to be achieved. In the present study, compared with cesarean section, vaginal delivery of selected breech infants at or near term was not associated with an increased neonatal morbidity or mortality rate.

The role of x-ray pelvimetry in breech delivery at term is controversial because normal measurements do not guarantee an easy vaginal delivery.[4, 8] Currently x-ray pelvimetry is used to identify patients with contracted pelvic dimensions and to preclude a dangerous trial of labor. Beischer[15] clearly established that vaginal breech delivery through a contracted maternal pelvis is associated with an increased risk of neonatal morbidity and death. None of the patients in this study with contracted x-ray pelvimetry were allowed vaginal delivery.

Estimating fetal weight in breech infants is frequently difficult. Fundal height and Leopold maneuvers were used to obtain an estimated fetal weight during the present study. In the extremes of the weight ranges, where weight criteria are critical, the accuracy of clinical weight estimation was decreased. Ultrasonography may now provide a new tool for evaluating fetal weights in utero, particularly identifying the infant with macrosomia. Any macrosomic fetus should probably be delivered by cesarean section to avoid the increase in perinatal morbidity and mortality associated with vaginal breech delivery of excessively large infants.

Oxytocin augmentation of breech labor remains controversial. Its use has been reported to be associated with an increase in perinatal morbidity and mortality.[5] However, the retrospective study by Rovinsky et al.[8] and the prospective, randomized trial by Collea et al.[3] did not associate labor augmentation with increased maternal or neonatal complications. The objective assessment of fetal well-being and quantitative evaluation of the progress of labor with Friedman curves has increased the obstetrician's awareness of early abnormalities of labor and allows appropriate intervention with labor augmentation or abdominal delivery. Careful evaluation to discern the cause of labor dysfunction must be accomplished before any augmentation of labor. Oxytocin augmentation of dysfunctional labor was used safely during the present study in carefully selected and monitored patients.

Maternal parity has been a major consideration in the management of breech delivery, in particular the frequent exclusion of the primiparous mother with a breech infant from a trial of labor because of the lack of a "proven pelvis." Multiple authors have found that perinatal morbidity and mortality are actually increased in multiparous patients.[4, 5, 8] Rovinsky et al.[8] related the disparity of worsened outcome in the multiparous patient to the observation that primiparous patients are considered higher risk than are multiparous patients and therefore are monitored more critically. The multiparous patient with a "proved pelvis" may not be evaluated and observed as critically or diligently. Maternal parity alone probably should not exclude a patient from consideration and evaluation for a trial of labor and vaginal breech delivery.

With the rise in the rate for cesarean section for term as well as preterm breech presentation, careful consideration must be given to maternal morbidity and mortality directly related to cesarean delivery. This issue has even greater consequences when repeat cesarean sections are performed frequently for delivery of subsequent pregnancies. The study by the National Institutes of Health of cesarean section[16] reported that the rise in the rate of cesarean sections for breech presentations between 1970 and 1978 was from 11.6% to 60.1% nationally. Cesarean section for breech presentations contributed 10% to 15% of the overall total rise in the rate of cesarean sections during that period.

This same National Institutes of Health study reported a maternal mortality rate related to cesarean section of 9.9 per 100,000 births in 1978.[16] This represents a twofold to fourfold increased risk of maternal death with cesarean delivery when compared with vaginal delivery. Although the risk of maternal death is quite small, significant maternal morbidity related to operative cesarean delivery occurs in 33% to 50% of cases. The National Institutes of Health report in 1981[16] recommended that "vaginal delivery of the term breech should remain an acceptable obstetric choice for delivery" when certain criteria are satisfied. Rovinsky et al.[8] conclude, "Unless and until elective cesarean section is shown to be as safe for the mother as vaginal delivery, routine elective cesarean section remains an unsatisfactory solution to the problems posed by term breech vaginal delivery." In their prospective, randomized study, Collea et al.[3] reported 208 term, frank breech infants with a 29% vaginal delivery rate and concluded that vaginal breech delivery of selected patients is a reasonable alternative to routine, elective cesarean sections. Acknowledging these significant maternal risks from operative delivery, one must carefully consider the recommendation of routine cesarean section for all term and near-term breech infants.

The retrospective nature of this study, the lack of a prospective written protocol of management, and the absence of long-term intellectual and developmental follow-up of these children are recognized.

However, based on the results of the present study of this patient population and a review of the obstetric literature, the authors present a possible protocol (Table V) for the prospective selection and intrapartum management of patients being evaluated for a trial of labor with breech presentations.

Our data support that if the mother-infant pair and hospital situation are selected carefully, parturients with term and near-term frank and complete breech presentations may safely be allowed a trial of labor and vaginal delivery with minimal risk of fetal asphyxia or delivery trauma. At the same time the risk of maternal complications related to cesarean section may be reduced. Use of cesarean section for all breech presentations is associated with a major risk of maternal morbidity and even some mortality while not necessarily eliminating fetal asphyxia, trauma, or neonatal complications. This study supports some movement of current obstetric management toward vaginal breech delivery of selected patients. More important, these data may form a basis for additional, large, prospective, randomized trials of vaginal breech delivery of the term and near-term infant and for detailed long-term follow-up of those children delivered according to modern obstetric standards.

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Discussion

DR. PETER E. FEHR, Minneapolis, Minnesota. I would like to ask the authors some questions concerning their results and comment on the presentation using some data from a recent study we reported in *Minnesota Medicine*.[1] Twenty-three fetuses were noted to have hyperextension of the head, I presume diagnosed by roentgenography. It is difficult to determine if these were 23 of the 180 considered to be candidates for vaginal delivery on the basis of adequate x-ray pelvic measurements or whether these were 23 of the 334 evaluated for vaginal delivery by roentgenography.

It is stated that 135 patients were delivered vaginally and I would question whether this is the 135 of the 180 who were felt to have adequate x-ray pelvic measurements. If this is the case, this is an extremely high success rate for vaginal delivery in patients meeting the criteria and the authors are to be commended.

Several areas of the study cause a great deal of concern. One area is the extremely high rate of vertical uterine incisions. The authors report a 27% vertical incision rate plus some T incisions, which means that these patients are automatic candidates for repeat cesarean sections in the future. Although most authors report an increase in the rate of vertical uterine incisions for the protection of the fetus, since these were term-size fetuses and the lower uterine segment should have been well developed, I question the need for this high percentage. Our study showed a 2% vertical incision rate with no fetal injuries as a result of cesarean delivery, so I would ask what the reason was for the high rate of vertical uterine incisions. In addition, it is noted that 87% of the cesarean sections were performed under general anesthesia. Is this standard procedure for your area or is there some reason this type of anesthesia was chosen?

Also of concern are two major fetal injuries that occur with delivery by cesarean section, a brachial plexus injury and a fractured femur. One must question the handling of the infants at the time of delivery through the uterine incision to have such major injuries resulting at cesarean section. Certainly one would have to question the statement in their comment section that if you cannot proceed with vaginal delivery, you could have an "atraumatic" cesarean section.

Did the 31% rate of endoparametritis reported in this study occur before the use of prophylactic antibiotics or did they occur in spite of their use?

In our retrospective review, one of the greatest problems we found was the clinician's decision to attempt a vaginal delivery in a multiparous woman without x-ray pelvimetry because the patient had a "proved pelvis" by having a previous vaginal delivery. In our x-ray pelvimetry reviews we found that when multiparous patients did have x-ray pelvimetry, 40% were considered inadequate for breech vaginal delivery and 45% of primigravid patients were considered inadequate. One of the concerns we had was that 50% of the patients who were delivered vaginally did not have x-ray pelvimetry and 10% of the patients who were delivered vaginally had known inadequate x-ray pelvic measurements.

Did any vaginal breech deliveries occur during this time in your hospital other than those you call "emergency" vaginal deliveries that did not have x-ray pelvic measurements and other evaluations? If so, what were their outcomes?

In the Comment section the authors mention maternal weight as being a factor; however, it is not mentioned at all in the Results section. I am wondering whether the authors have any data on maternal weights in these cases. If these were available, how did they affect the outcome of these cases?

In closing I would like to concur strongly with the authors that with the incidence of precipitate breech deliveries it is essential that we train people in the management of the vaginal breech delivery. If they are not trained in vaginal breech deliveries, they are not going to be able to manage the second twin, who may present as a transverse or breech, thus requiring a cesarean section fairly routinely for second twins or multiple gestations in general. I concur with the authors' conclusions, which agree with those of our study, which show that in selected cases vaginal breech delivery can be carried out safely. I think that in view of the concerns about the rising rate of cesarean section and costs of medical care we should consider this matter carefully.

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DR. BROOKS RANNEY, Yankton, South Dakota. Dr. Tatum and his coauthors have outlined the evolution in management of breech presentation at term, made comparisons of the fetal and maternal outcome after emergency vaginal delivery, planned vaginal delivery, and cesarean section delivery, and discussed the implications of their findings. This thorough study limits the range for discussants.

However, as the authors have implied, no large-scale study can evaluate the specific knowledge, training, experience, skills, reflexes, and gentle sense of touch of individual obstetric operators. A breech fetus that might be delivered best vaginally by a consummate obstetrician may be delivered more safely by cesarean section by a less skillful obstetrician. Therefore a study such as this portrays the average situation in a specific medical environment, but it may not apply to all medical environments. For instance, we agree with the "general selection criteria for a trial labor," propounded by the authors, with the exception that because our population has a majority of Nordic, Germanic, and Native American women, who have larger pelves, we would raise the upper limits of estimated fetal size for planned vaginal delivery to about 4200 gm.

In 1965, Zatuchni and Andros reported on a scoring system to help predict safe vaginal delivery of the breech fetus using parity, gestational age, estimated fetal weight, previous breech deliveries, dilatation, and station. In 1974, Bird and McElin used this system not only to predict which breech fetuses could be delivered safely vaginally but also to predict which dysfunctional labors could be augmented by "cautious stimulation with intravenous oxytocin." I have never used intravenous oxytocin in the presence of breech presentation; but (according to "general selection criteria . . .") Dr. Tatum and his co-workers monitored the fetuses electronically and augmented dysfunctional labors effectively 78% of the time, when needed.

The authors have noted that cesarean section does not always prevent manipulative delivery or birth injuries. In this regard the routine use of the low transverse cervical section incision can be dangerous to the fetus and/or mother. When manipulative delivery from certain breech presentations is anticipated, the obstetrician sometimes may choose low vertical cervical section because it can be extended either up into the myometrium or down into the vagina with less danger to maternal arteries and ureters and with more space for fetal manipulation.

The reported 29% incidence of third- or fourth-degree perineal lacerations associated with vaginal deliveries of breech fetuses is unnecessarily high. These usually can be avoided by performing a pudendal block to relax perineal musculature and by the use of adequate and timely mediolateral episiotomy.

During delivery of the after-coming fetal head the key word is flexion. Immediately after delivery of the shoulders the obstetrician may allow the baby's torso to straddle the forearm and place an index finger in the fetal mouth, pulling downward on the mandible to maintain complete flexion of the fetal head. Then with the fetal occiput against the fulcrum of the maternal pubis, the fetal head may be rolled gently up and out of the pelvic outlet with very little traction on the fetal neck. We always have Piper forceps open and ready on the delivery table but have needed them only twice.

Twelve years ago I reported to this association my results in preventing breech presentation (and possibly preventing prematurity) by use of external cephalic version, starting at 28 to 30 weeks of gestation. However, despite skillful external version, about one in six such fetuses will remain in breech presentation at term, and others will be referred during emergency labors. Among 6000 obstetric deliveries performed by me between 1948 and 1975, 59 patients in labor had single breech fetuses (about 1%). Of these, 34 had been referred during labor. Five weighed less than 2000 gm, 43 weighed between 2000 and 4000 gm, and 11 weighed more than 4000 gm. Forty-five were delivered spontaneously to the umbilicus with manipulation as needed for the legs, after-coming shoulders, and head, five were delivered by breech extraction, and nine were delivered by cesarean section. Pudendal block anesthesia was used for 43 of the vaginal deliveries and local block anesthesia of the abdominal wall was used for eight of the cesarean sections. Four neonates died of severe congenital anomalies of the urinary system, incompatible with life. There were no other perinatal deaths. Tracheal catheter resuscitation was used for six of the 59 infants, three of which weighed less than 2000 gm. All responded well. Six breech babies were found in congenitally anomalous, unilaterally narrow uteri. Since we practice in a small city, surrounded by a large, stable farm population from which few people move, most of these infants had received their pediatric care for years from two pediatricians with whom we work in close association. Under these circumstances, I would know if significant neurologic sequelae had been noted, and there have been none.

Those among you who have been singed by the unpredictable lightning of medical liability may be incensed because I have not yet discussed its effect on choice of breech delivery, for it truly is not part of a scientific discussion. However, if you live in a particularly murky medical liability climate, the practicing clinician cannot ignore this aspect. Therefore more mothers undergo cesarean sections rather than vaginal deliveries, with a consequent increase in maternal morbidity and uterine scars and with not necessarily better results for the infants. This study should be of some assistance to those who choose to use obstetric judgment and skill rather than medical liability hazard while determining quality care for their obstetric patients.

There are two questions for the authors: First, among the 9% of infants that were identified as "small for gestational age," do you know how many had been nourished by a low-lying placenta, or placenta previa, or had been harbored within a congenitally abnormal, narrow, unilateral uterus? Second, how often was incomplete breech presentation associated with congenital anomalies of the fetus?

Dr. Stacy R. Stephens, Dallas, Texas. I have two questions for the authors.

First, did the gravidity of the patient make any difference in your selection of cesarean section versus vaginal delivery? Second, in Birmingham, is this endometritis rate of 31% and a transfusion rate of 8.9%

peculiar to the mothers delivered by cesarean section for breech delivery, or is this what you have on your service as a whole?

Dr. John C. Morrison, Jackson, Mississippi. I would like to ask Dr. Tatum and his coauthors about the two injuries that occurred during cesarean birth, and were those incisions vertical?

We would certainly agree that usually the abdominal delivery of a breech infant would mandate a vertical incision in most cases. Three years ago, before this association, we presented, in cooperation with the group in Birmingham, data that would suggest in the vaginal delivery, after a prior abdominal incision, that vertical incisions in the uterus, although not classical, were not associated with an increased tendency to rupture.

Dr. Mortimer G. Rosen, Cleveland, Ohio. I congratulate Dr. Tatum and coauthors and hope that this is another article in the literature that will allow at least some freedom of choice for birth route in breech presentation.

My questions for the authors are several: Why did you choose 2000 gm as the weight limit and what happened below this birth weight?

My reason for asking the questions reflects some of the work we have published or have in press that includes mortality rates, morbidity in the neonatal period, morbidity through 2 years of life, and individual examination of every brain-damaged infant at all birth weights in 500 gm increments beginning at 500 gm. There were no differences in outcome for the breech presentation delivered by cesarean section as compared with the breech presentation delivered vaginally at all the birth weights both below and above 2000 gm, as long as the fetus was alive on admission and had no major congenital abnormalities.

Once again, the reason for asking that question is that, if noted after delivery, low birth weight with its higher incidence of breech presentation is not as morbid as we thought in the past; it becomes easier for the obstetrician to identify that you do not have to make the choice of birth route based on birth weight. Birth weight is difficult to predict. Birth route change contributes little to the outcome in these infants.

Dr. John A. Garbaciak, Jr., Cleveland, Ohio. I would like to ask Dr. Tatum two questions. When you estimate fetal weight, do you do that clinically or do you take time to do it ultrasonographically, and also with regard to the performance of pelvimetry, what method did you use? What criteria did you use to judge adequacy or inadequacy, and could you comment on the patient who may have returned from pelvimetry with inadequate measurements and needed to be delivered vaginally?

Dr. Tatum (Closing). Dr. Fehr raised several questions. In reference to the incidence of hyperextension of the fetal head, this was identified in 23 of the 334 patients who had abdominal x-ray films as part of their prelabor evaluation, for an incidence of 7%.

Concerning the role of x-ray pelvimetry, 135 vaginal deliveries were achieved in patients selected for a trial of labor after initial evaluation, including x-ray pelvimetry. An additional 39 patients, for a total of 174, had precipitate vaginal deliveries before detailed evaluation because of advanced stages of labor. All of the 135 women with planned vaginal deliveries had noncontracted x-ray pelvimetry; no vaginal deliveries occurred in patients with identified contracted pelvic dimensions.

Vertical uterine incision was performed in 27% of cesarean sections. This frequence reflects the lack of development of the lower uterine segment when abdominal delivery was performed on patients, particularly with ruptured membranes or incomplete breech presentations before significant labor.

The 87% rate for general anesthesia for cesarean section is high. In the larger of the two obstetric units involved in this study, regional anesthesia was not available for cesarean sections. Also, 39 patients required emergency abdominal delivery on presentation, which generally precluded regional techniques.

The 31% incidence of endoparametritis during the study period from 1976 through 1982 occurred with the intermittent use of prophylactic antibiotics. This rate was fairly constant during the study period, independent of the indications for operation, and probably reflects the generally lower socioeconomic status of our patient population.

In reference to Dr. Ranney's question about the association of infants small for gestational age with anomalies of placental location or uterine anomalies, I was unable to isolate that information from our data. However, 32% of the infants who were small for gestational age were delivered vaginally. Of those infants with congenital anomalies, the distribution of these anomalies followed the pattern of distribution of breech configurations over the entire study population. Congenital anomalies were found in 6.3% of the incomplete breech presentations.

Dr. Morrison asked about the type of uterine incision associated with the injuries at cesarean section. In both cases it was a transverse lower uterine segment incision. This reemphasizes an important point, that if cesarean section is to be used in an attempt to avoid birth trauma, the uterine incision must be adequately large to allow atraumatic delivery with a liberal use of vertical incisions when the lower uterine segment is not well developed.

Dr. Stephens asked about the role of parity in the management of the study population. Although there was a significant difference in the rate of vaginal delivery for primiparous patients at 22% and multiparous patients at 32%, careful review of the indications for cesarean section in the primiparous mothers revealed that only 2.8% of the cesarean sections were performed for primiparity as the singular indication.

Dr. Rosen asked how the 2000 gm lower limit for weight was chosen. This was somewhat arbitrary and reflected the general opinion of the staff physicians, that the concept of "premature breech" began to apply below about 2000 gm. In a review of the medical records for study selection, it was found that the neonatal complications below 2000 gm greatly reflected the consequences of prematurity, primarily respiratory distress syndrome and its associated complications.

Dr. Garbaciak asked how the fetal weights were evaluated. The fetal weights were estimated according to standard clinical parameters. Although we have included possible use of ultrasonography in our proposed protocol to assist in evaluation of the fetal weights, this was not used regularly during the study. Its use does have merit, particularly in identifying the macrostomic infant and therefore precluding a possible dangerous trial of labor.

Concerning x-ray pelvimetric parameters, several sets of values appear in the literature. The minimum values probably are those quoted by Dr. Collea from California. We propose to use slightly larger measurements shown on the protocol tables, as these have also been used multiple times in the literature on this subject.

Flow velocity waveforms in the maternal uteroplacental and fetal umbilical placental circulations

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A simple continuous-wave Doppler ultrasound system was used to record arterial flow velocity time waveforms from branches of the maternal uterine artery in the placental bed and the fetal umbilical arteries. The systolic-diastolic ratio of flow velocities was measured as an index of peripheral resistance. In normal pregnancy both circulations exhibit high diastolic flow velocities caused by low resistance. The study group consisted of 172 pregnancies with high fetal risk of which 53 resulted in delivery of a small–for–gestational age infant. The last study-to-delivery interval was <10 days. In the small–for–gestational age fetuses in whom both umbilical and uterine studies were normal there was good fetal outcome (19 cases). Neonatal morbidity occurred among those with abnormal umbilical studies with low diastolic flow velocities, indicating high resistance. Of these studies there were two subgroups. An abnormal uterine study (13 cases) indicated a primary maternal uteroplacental lesion and a normal study (21 cases) a primary fetal lesion. In cases of severe maternal hypertension, abnormal uterine artery waveforms were associated with abnormal umbilical artery waveforms. (AM J OBSTET GYNECOL 1985;152:155-63.)

Key words: Uterine placental blood flow, umbilical blood flow, Doppler ultrasound, flow velocity waveforms

Placentation brings into contact the fetal umbilical and maternal uterine circulations. Perfusion of these two beds must be in balance to optimize exchange. There is much speculation as to whether the fetus determines its placenta and uteroplacental blood flow or the uteroplacental flow constrains the fetus.[1] Inaccessibility of the human fetus has hitherto prevented examination of the placental circulations.

Doppler ultrasound may be used to study blood flow in deep-lying vessels. The moving column of red blood cells scatters and reflects an ultrasound beam with a frequency shift proportional to its velocity. This allows display of the flow velocity–time waveforms. Volume flow may be measured as the product of vessel area and mean velocity.[2,3] The flow velocity is influenced by the ejection systolic pulse, arterial wall compliance, blood stream inertia, and downstream peripheral resistance.[4,5] The ratio of systolic to diastolic flow velocities and the pulsatility index have been suggested as measures of the effect of resistance on the velocity waveform.[6]

The uterine placental[7] and umbilical placental[8,9] circulations are high flow low resistance vascular beds in which the increasing volume flow of pregnancy has been attributed to a decrease in resistance, not to a

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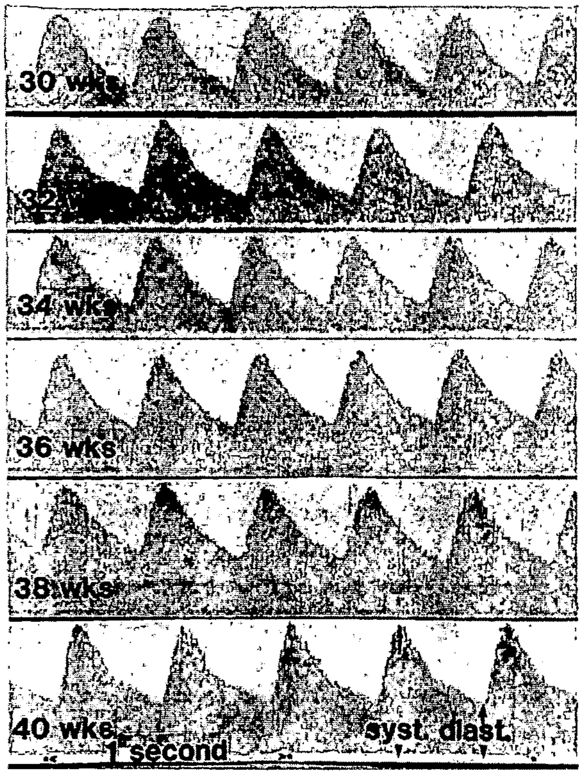

Fig. 1. Serial studies of the umbilical artery flow velocity–time waveforms in normal pregnancy from one patient.

Table I. Principal reasons for study of 172 complicated pregnancies

Principal reason for study	*No. of cases*
Suspected intrauterine growth retardation	88
Hypertension	36
Antepartum hemorrhage	7
Threatened premature labor	2
Diabetes	22
Renal disease	7
Rhesus isoimmunization	4
Miscellaneous	6
Total	172

pressure increase (flow = pressure/resistance). Methods of examining the flow velocity–time waveforms in both circulations with Doppler ultrasound have been described by us[10-13] and others.[14-17] In this study the relationships between these two circulations are examined in complicated pregnancy.

Material and methods

Patients. Serial studies were carried out in normal pregnancy. These results, which have been reported,[12, 13] were used to calculate normal limits for the systolic/diastolic ratio for both the umbilical artery in the cord (Fig. 1) and a placental bed branch of the maternal uterine artery in the placental bed (Fig. 2).

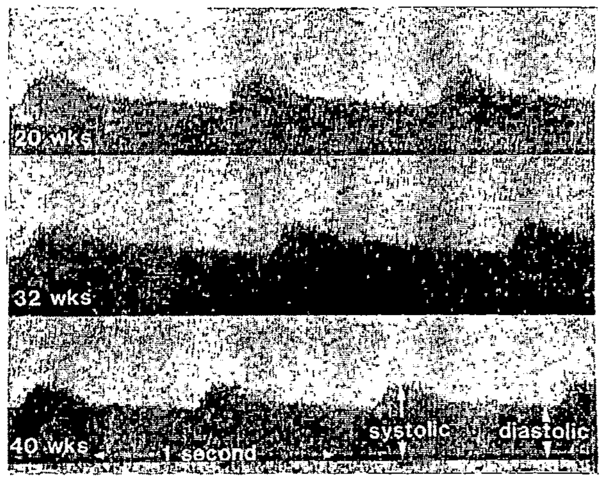

Fig. 2. Serial studies of the uterine artery flow velocity–time waveforms in normal pregnancy from one patient.

Uterine and umbilical artery waveforms were studied in 172 complicated pregnancies on 454 occasions. The group consisted of a consecutive series of patients referred to a fetal welfare laboratory for studies (including fetal heart rate monitoring) because of potential fetal risk in whom the last study was <10 days from delivery. The principal reason for study is shown in Table I. Patients were resting at the time of study and examined in a semirecumbent position. Studies during periods of fetal activity or breathing movements were not used.

Methods. A simple continuous-wave directional Doppler blood velocimeter was used to record the flow velocity–time waveforms. A 4 MHz transducer was used. The audible frequency shift signal was processed by a real-time spectrum analyzer and displayed on an oscilloscope. An oscilloscope recorder was used to provide a hard copy on light-sensitive paper. All studies were also recorded on audio tape to permit future reprocessing. Measurements were averaged from at least five waveforms. The average study time was 15 to 20 minutes. The power output of our system has been measured at 9 mW.

The umbilical artery in the cord was recognized by the characteristic shape of the velocity waveform on the oscilloscope (and sound) and the ability to simultaneously display flow in the umbilical vein in the opposite direction.

The maternal uterine artery was recorded from the uteroplacental bed. This was first located with a B-mode real-time scanner, and the continuous wave transducer then searched to identify the vessel. These recordings were made from a radial or arcuate branch of the uterine artery in the placental bed.

For both umbilical and uterine waveform recordings we validated our simple continuous-wave Doppler system by use of a combined pulsed Doppler B-mode sys-

Table II. Pregnancy outcome and study results

	Total cases	*Umbilical artery waveform studies*		*Uterine artery waveform studies*	
		Normal	*Abnormal*	*Normal*	*Abnormal*
All patients	172	110	62	131	41
Bad fetal outcome					
Neonatal deaths	12	2	10	6	6
5 min Apgar score <7	13	5	8	5	8
Birth weight less than tenth percentile	53	19	34	35	18
Subtotal	63	24	39	39	24
Good fetal outcome	109	86	23	92	17

tem which allows precise location of a sample volume for Doppler recording on a B-mode image. Interobserver variation was <15%. It was shown that time of day was not important provided the patient was resting.

The flow velocity–time waveforms were examined visually and quantitated by use of the systolic/diastolic ratio. This was measured as the ratio of peak systolic flow velocity to least diastolic flow velocity (See Figs. 1 and 2).

Results

In normal pregnancy both the umbilical and uterine artery waveforms show high diastolic flow velocities indicative of low downstream resistance (Figs. 1 and 2).

The last study results for both fetal umbilical artery and maternal uteroplacental bed artery waveforms were tabulated by fetal outcome (Table II). No fetus died in utero. Poor fetal outcome was better predicted by an abnormal fetal umbilical artery study (39 of 63) than maternal uterine study (24 of 63) ($p < 0.01$, χ^2 test).

Fifty-three fetuses delivered were small for gestational age (Table III). The fetuses with an abnormal umbilical study were delivered earlier ($p < 0.01$) and were more likely to require neonatal intensive care admission ($p < 0.001$). The last umbilical studies in this group are shown in Fig. 3 along with an indication of the uterine study result. Early delivery is associated with a high ratio. The small–for–gestational age fetuses were thus divisible into three groups: those with normal umbilical and uterine studies and not admitted to neonatal intensive care, those with abnormal umbilical normal uterine studies and requiring neonatal intensive care, and those with abnormal umbilical abnormal uterine studies and requiring neonatal intensive care. The results of uterine studies in this small–for–gestational age group are shown in Fig. 4. In 18 of the 53 patients the study results were abnormal. Where the uterine systolic/diastolic ratio was very high (>3), the umbilical waveform was abnormal. Representative case studies are shown in Figs. 5 and 6. The waveforms and fetal heart rate monitoring traces were the last studies before delivery.

Table III. Results of study in the group of 53 small–for–gestational age fetuses

	Umbilical artery waveforms	
	Normal	*Abnormal*
No. of fetuses	19	34
Uterine artery waveform		
Normal (n)	14	21
Abnormal (n)	5	13
Mean gestational age at delivery (wk)	37.6	34.6
Normal uterine waveform	39.0	34.4
Abnormal uterine waveform	35.4	35.0
Admission to neonatal intensive care (n)	3	23
Normal uterine waveform	1	13
Abnormal uterine waveform	2	10
Neonatal deaths (n)	0	6
Normal uterine waveform	0	1
Abnormal uterine waveform	0	5

In the assessment of the results from the whole group (Table II) it is apparent that fetal morbidity occurred with a normal umbilical study in 24 cases. Nineteen of this group were small for gestational age, but only three required neonatal support (two had a low Apgar score). The two neonatal deaths were due to prematurity in association with rhesus isoimmunization and multiple congenital abnormalities. Uterine studies were not a sensitive predictor of poor fetal outcome but did serve to divide all cases in a manner similar to the small–for–gestational age subgroup.

In 38 of the patients, maternal hypertension was noted; in 35 this was considered the principal reason for study. Twenty-three patients were classified as severely hypertensive with diastolic blood pressure >110 mm Hg and proteinuria >1 gm/day. In 17 patients the umbilical artery study was abnormal. The uterine study was abnormal in 11 cases; 10 cases also had an abnormal umbilical study, again indicating the association be-

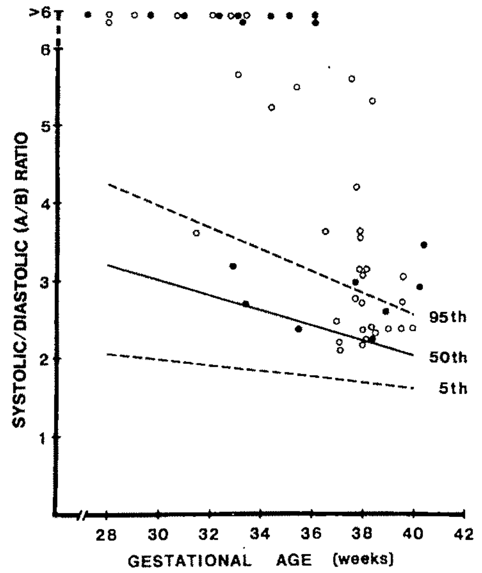

Fig. 3. The umbilical artery waveform in the last study of the group of fetuses who were small for gestational age when subsequently delivered was divided by the results of the uteroplacental waveform. *Solid dot,* Abnormal uterine artery waveform; *open dot,* normal uterine artery waveform.

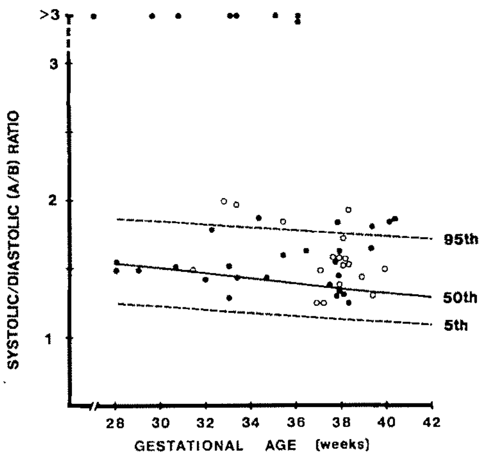

Fig. 4. The uterine artery waveform in the last study of the group of fetuses who were small for gestational age when subsequently delivered was divided by the umbilical studies. *Solid dot,* Abnormal umbilical artery waveform; *open dot,* normal umbilical waveform.

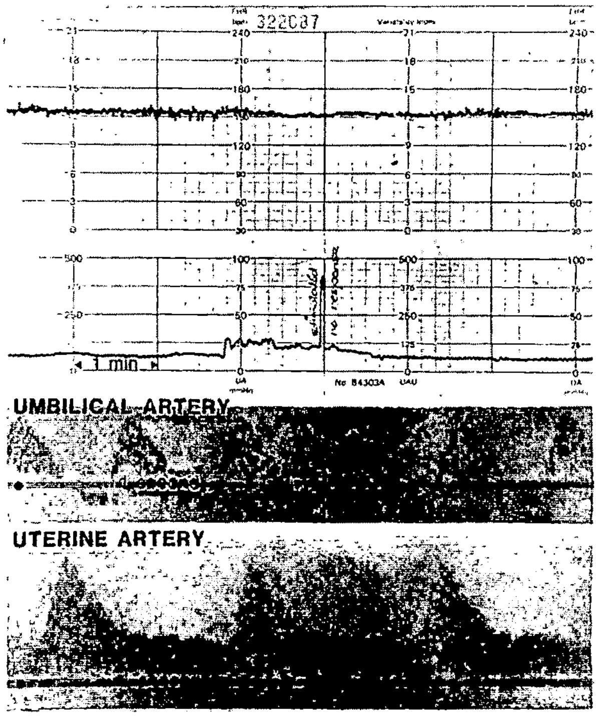

Fig. 5. A case study demonstrating an abnormal umbilical and uterine waveform in association with severe growth retardation. In the umbilical study there is reversed flow in diastole. The uterine waveform shows reduced diastolic flow velocity. Patient was 30-year-old woman, para 0, gravida 2, who was delivered by low-segment cesarean section at 35 weeks because of decreased fetal movement. Female infant weighed 1590 gm and placenta 454 gm.

tween abnormal uterine and umbilical artery waveforms. Of the 23 cases with no fetal morbidity and with abnormal umbilical studies (Table II) seven had severe hypertension. In contrast, only five of the 86 cases with no fetal morbidity and normal umbilical studies had severe hypertension ($p < 0.01$).

Serial studies from a patient affected by systemic lupus erythematosus with renal involvement are shown in Fig. 7. Concern about fetal welfare led to delivery at 35 weeks. The uterine waveforms were abnormal from early in pregnancy. Only from 30 weeks does the umbilical artery waveform show decreasing diastolic flow velocity, which suggests uterine abnormality leading to fetal umbilical effect.

Comment

Arterial flow velocity waveforms may be recorded with use of simple continuous-wave Doppler ultrasound, and this system is very suitable for widespread application in obstetrics. The systolic/diastolic ratio is a readily measured parameter that is useful in quantitating peripheral resistance. The systolic ejection pressure pulse travels down the arterial tree to the periphery. Wave reflection occurs at arterial branches and at the small arterial/arteriolar peripheral resistance vessels. The degree of reflection (reflection coefficient) is determined by peripheral resistance. High resistance causes high reflection of the incident pressure wave so that the returning wave opposes and cancels the later part of the forward pressure pulse. This results in low diastolic flow velocity. Low resistance allows onward travel of the pressure wave with little alteration. High diastolic flow results.

Our observations in normal human pregnancy reveal

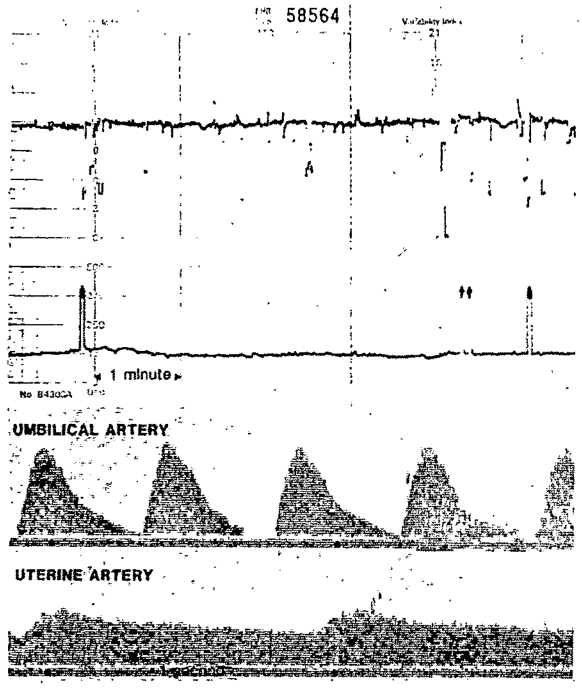

Fig. 6. A case study demonstrating an abnormal umbilical waveform in association with normal uterine artery waveform. Patient was 24-year-old woman, para 1, gravida 4, who was delivered by low-segment cesarean section at 30 weeks because ultrasound studies showed marked placental degeneration. Female infant weighed 790 gm and was taken home after 11 weeks.

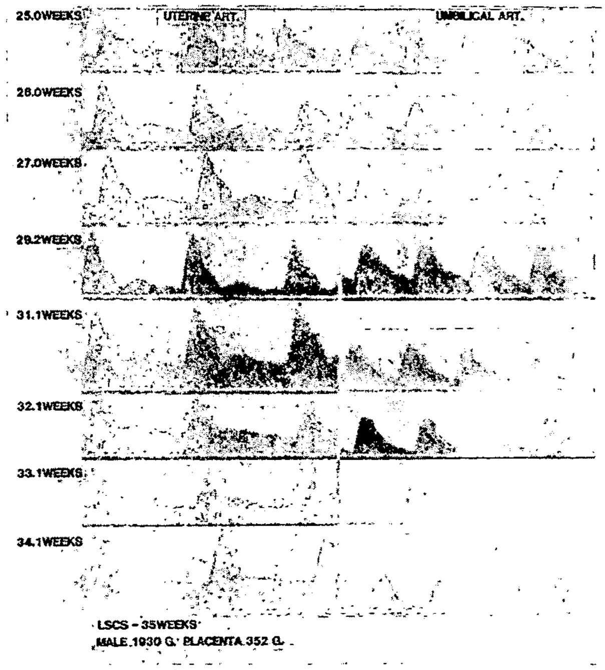

Fig. 7. Serial studies in a 25-year-old patient, gravida 2, para 1, with systemic lupus erythematosus, for which she received 3 mg/day of prednisone as well as oxprenolol for hypertension. She was delivered at 35 weeks by low-segment cesarean section of a 1930 gm male infant. Placenta weighed 352 gm.

high diastolic flow velocities in both the maternal uterine and fetal umbilical systems. This has been directly measured in ovine pregnancy.[7-9] A parameter that measures flow resistance becomes especially valuable as a noninvasive index of blood flow, since in these beds resistance is a major determinant of flow.

In this paper a group of patients in whom the fetus was considered at high risk were studied. The absence of intrauterine death in this series reflects intensive surveillance and a policy of early delivery in the presence of preterminal fetal heart rate monitoring. Among the group of fetuses that were small for gestational age at delivery, studies of uterine and umbilical artery flow velocity waveforms permitted three broad divisions. It is suggested that the subgroup with normal umbilical and uterine artery waveforms are not at risk of fetal morbidity and may represent a group with uncomplicated low growth potential. These fetuses did not require neonatal intensive care and were delivered later. The others in the small–for–gestational age group are characterized by abnormal umbilical artery waveforms indicative of high resistance. In these patients the uterine artery velocity waveforms were either normal (Fig. 6) or indicative of high resistance (Fig. 5). Neonatal morbidity was present in both of these subgroups. In patients with a normal uterine pattern the primary defect is on the fetal side of the placenta. Although the uterine waveform is normal, indicating normal resistance in that branch of the uterine artery, total uterine flow may be low if the size of the uteroplacental bed (and number of branches of the uterine artery feeding it), as determined by placental growth, is not extensive. Those fetuses with low umbilical and uteroplacental diastolic flow velocities may represent a group of fetuses in whom vascular disease exists in the maternal uteroplacental bed and constrains the placenta and fetus. Serial studies in some cases (Fig. 7) support this concept. High uteroplacental ratios were associated with high umbilical placental ratios, and this was particularly true in cases of severe hypertension. The fetal placenta is nourished by the maternal uteroplacental circulation,[18] and this may be the mechanism of effect on the umbilical placental circulation. In the cases with abnormal umbilical artery waveform but "good" fetal outcome, there may be a circulatory effect not yet manifest on the fetus. Especially in the severely hypertensive group, the vascular problem may be relatively acute so that poor fetal outcome resulting from chronic fetal deprivation has not occurred.

A study has been carried out to relate umbilical artery flow velocity waveforms to placental microvascular anatomy.[19] High systolic/diastolic ratios were associated with an obliteration of the small arteries and arterioles in the tertiary villi of the placenta. These are the vessels of resistance across which the pressure drops in the placenta.

These findings contribute to the management of the high-risk fetus. Growth retardation associated with fetal morbidity is predicted by the umbilical artery velocity waveform. It is possible to more precisely define placental perfusion disturbances on both fetal and maternal sides operating in fetal compromise. In a mother with underlying vascular disease, prediction for the fetus at risk may be made before compromise to allow intensive surveillance and vigorous specific maternal therapy.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. HAROLD SCHULMAN, Mineola, New York. It is my belief that umbilical artery velocimetry will be a very important part of fetal surveillance by the end of this decade. There appears to be a number of exciting applications in addition to those mentioned today. For example, in twin pregnancies, it offers a powerful tool to delineate each fetal umbilical vascular resistance. Thus as early as the fourth month we will know whether placentation was equally partitioned or whether one twin was crowded out. In poorly controlled cases of diabetes the umbilical vascular resistance increases, which explains the mystery of why diabetic fetuses are so fragile as they approach term. There is also a hint that this technique may uncover the cause of unexplained stillbirths and premature labor, for example, a defective placental circulation.

Dr. Trudinger's data closely parallel ours, recently published, on growth retardation and hypertension.[1,2] In the study we heard today, there were 53 small–for–gestational age fetuses and 33, or 62%, who had elevated umbilical velocity wave ratios. From the neonatal data it can be suspected that the small–for–gestational age fetus with altered umbilical vascular resistance is the one most likely to be deprived of nutrients and ultimately of oxygen. Two broad categories of umbilical vascular resistance can be identified: one is associated with abnormal uterine velocity waveforms, and the second is an intrinsic placental angiogenesis problem. When abnormal uterine flow was suspected, 72% (13 of 18) had an elevated systolic/diastolic ratio. However, with normal uterine wave contours, there still appeared to be a placentation risk of 60% (21 of 35). This difference is not significant. However, if a different cutoff point were selected for an abnormal uterine artery value, such as >2, the data would be very significant. Perhaps a one-tailed significance test should be used.

There is much work to be done. Although four laboratories around the world appear to be obtaining comparable results, there are a number of potential pitfalls.[3,4] Dr. Trudinger mentioned that there must be a quiet fetus. When there is active fetal breathing, there is a sinus arrythmia that makes measurement of ratios difficult because the altering pulse intervals result in different diastolic velocity levels. We suspect that measurements of umbilical arteries made at the abdominal wall will demonstrate higher ratios than those further along in the cord. Also of importance is the number of measurements necessary for optimum results so that the effect of transducer angle can be minimized. For example, our standard deviation per week of gestation is 0.45 per ratio. Finally there may be significant differences in instrumentation. In Dr. Trudinger's 53 small–for–gestational age fetuses, 20 had little or no diastolic flow. In our first 27 cases we have seen only one, thus, there may be differences in the instrument's spectrum analysis or Doppler design or possibly the sites of measurement on the artery.

I think the uterine artery measurement is much more difficult and complex, although Trudinger's data are close to those arrived at by Campbell et al. There is a difference in the uterine hypogastric waveform compared to the arcuate-radial, and it is difficult to be sure which you are measuring. As the uterus grows larger, this becomes an even more difficult technical problem. I think it is solvable, but much more work is needed.

Finally, it should be pointed out that the approach described by Dr. Trudinger is umbilical velocimetry utilizing a pattern recognition technique. During the past 6 years a number of investigators have pursued this problem by attempting direct flow measurements on the umbilical vein. This approach is more time consuming, is fraught with error, and involves considerable more ultrasound exposure. It appears that the pattern recognition approach is as accurate in terms of sensitivity, specificity, and predictive value and offers the promise of being easily mastered by the practicing obstetrician. I think we can look forward to an enormous body of literature which will evaluate this new technologic innovation.

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DR. WILLIAM R. ANDERSON, Bloomington, Indiana. I want to congratulate Dr. Trudinger and his associates for receiving the Central Award for this timely and well-done paper. This work represents but a portion of the clinical and research output from the Fetal Welfare Laboratory at Westmead Hospital in Sydney, Australia. The study of flow velocity waveforms is a new concept to me. The laws of physics and the complex formulas that form the basis for determining flow velocities in vascular systems is well documented. The use of Doppler ultrasound systems to intercept various vascular arterial and venous channels and the equipment to quantify and ultimately display on an oscilloscope these patterns of flow have recently become available. The reproducibility of results from several different laboratories in different parts of the world lends confidence to the reliability of the technique and the equipment.

The use of a ratio of systolic peak to diastolic levels obviates most of the technique areas of scanning error. The two areas being assessed in this paper have been shown by the present author and others to represent in a normal pregnancy, circulations with high diastolic flow velocities caused by a lowering peripheral resistance. This paper deals with a study group of 172 high-risk pregnancies, 53 of whom delivered small–for–gestational age infants. A comparison of waveforms, umbilical artery/uterine artery, has been presented.

In the figures presented the umbilical artery waveforms were the best predictor of fetal well-being; however, some infants with normal umbilical artery waveforms did have poor outcome, that is, two fetal deaths and three admissions to a neonatal intensive care unit. Were other than cardio-respiratory problems responsible for these unexpected "bad fetal outcomes"? A relationship of the two placental circulations (maternal/uterine artery, fetal/umbilical artery) is suggested in the severely hypertensive patient group. The independence of these two circulations in other cases is fascinating. Whether, on the basis of these data, a primary maternal or fetal cause of the bad neonatal outcome can be assigned still remains to be proved.

As a clinician I ask Dr. Trudinger the following questions: (1) Are you using this information prospectively in caring for high-risk patients? (2) Do you envision this technique becoming standard for evaluation of high-risk pregnancies? If so, what costs do you envision for the equipment and what level of sophistication/training will be necessary to effectively utilize such equipment?

DR. THOMAS H. KIRSCHBAUM, Bethesda, Maryland. I would like to ask you a couple of questions that have to do with the difficulties of making inferences about resistance and therefore flow from velocity profiles in general.

It seems to me, if you were to take the oscillating Doppler signals that you have shown here and the nadir of the diastolic velocity were to drop, blood flow might well be maintained, depending on what happened to the profile of the curve between the maximum and the minimum. That is, if there were a time shift in the area under the curve so as to have a preponderance of that area closer to the maximum coincident with the systolic impulse without materially changing the area you would predict a change in blood flow in what might only be a change in time-distribution of constant flow in the cardiac cycle. I wonder if I am incorrect in that.

Second, there are inferences of constancy embedded in a number of variables that are very difficult to hold constant.

The velocity of pulsatile flow down a straight vessel as a function of time is a sensitive function of distance from the vessel wall where it is zero to the middle of the vessel where it is maximally fast. In addition, the characteristic of the Doppler signal depends on the shape of the Doppler field, the geometry of the sensor, and the relationship of the Doppler geometry to the vessel being monitored. If the vessel twists or turns or if there is intravascular turbulence for other reasons, then I think the theoretical interpretation of what is being read down the wire from the Doppler sensor falls apart.

How did you maintain constancy in these variables during the duration of gestation, and how sure are you that they were the same in small-for-gestational age infants and normal infants at term?

Dr. Federico G. Mariona, Detroit, Michigan. Dr. Trudinger, can you estimate the total amount of sonic energy between real-time and Doppler signals that the average fetus receives during one of your flow studies, and also, can you differentiate a flow pattern indicative of acute fetal distress as opposed to chronic distress?

Dr. John A. Garbaciak, Cleveland, Ohio. I would like to ask the authors whether they defined a fourth group, that is, patients that had or exhibited abnormal uterine artery flow but also exhibited normal umbilical blood flow.

Dr. Norman F. Gant, Dallas, Texas. I would like to congratulate the authors on an interesting study, but the overall design and the interpretation of the results leave me a little confused.

Did I understand Dr. Trudinger to say that the babies were delivered as soon as abnormality was detected? And if so, did we not fail to see the natural progression of the various diseases he is describing? In other words, do we not have a self-fulfilling prophecy? If I deliver all babies at 27 weeks, there will be few stillbirths but very many consequences in a sick-baby nursery.

So my questions are, What were the criteria used to deliver these patients? Was the decision strictly based upon the waveforms you observed, or was it based upon waveforms plus clinical indications?

Dr. Trudinger (Closing). I would like to consider first the relationship between pressure, flow, and resistance. The volume flow at a point in the circulation is determined by the pressure gradient at that point. Resistance may be defined as mean pressure divided by mean flow over one cardiac cycle. We are studying the flow velocity–time waveform. Flow is the summation of all of the flow velocities across the vessel lumen during the time unit. The Doppler frequency waveform represents all of these velocities. In our analysis we have used the maximum envelope of the waveform representing maximum flow velocity. This waveform has been analyzed for a parameter that represents downstream peripheral resistance. Peripheral resistance determines the degree of the waveform reflection at the small artery/arteriolar level.[1] High resistance is associated with a high reflection coefficient so that the reflected wave reduces the level of flow in diastole. This leads to low diastolic flow velocities and in consequence a high systolic/diastolic velocity ratio.

It is possible to increase resistance and yet maintain flow by increasing heart rate or stroke volume. We have observed this in studies in fetal lambs. I think this is one of the explanations for the fact that measures of total umbilical vein volume flow have not proved to be a good indicator of fetal condition.[2] The compromised fetus is able to maintain volume flow until relatively late.

Dr. Schulman mentioned the question of twin pregnancies. We have reported on a series of 76 twin pregnancies.[3] Discordancy in weight is recognized by discordant umbilical artery waveforms. Here there is an opportunity to study two umbilical circulations of two fetuses who share the same placental bed, although they may not share it equally. Discordancy does suggest that it is a fetal lesion leading to the effect on growth, rather than a maternal uterine problem affecting the fetus.

It is most important that studies are carried out during periods when the fetus is quiet. Fetal breathing movements and fetal trunk and limb activity do affect the waveforms. It is for this reason that a strip of at least 10 seconds of waveform is recorded to ensure that the fetus is being studied in a resting state.

The cases reported in this presentation were very definitely a "high risk" group referred to a tertiary care center. It is for this reason that the number of obstetric abnormalities is high, and indeed it was our intention to contrast the normal and very abnormal.

To again return to the question of the difference between velocity waveform and volume flow, I would like to point out a fundamental difference in the uterine and umbilical recording. On the uterine side, we are looking at waveforms from one branch of the uterine artery (either a radial or arcuate vessel) in the placental bed. There are perhaps 150 such vessels in an average placental bed. We believe we are looking at placental bed pathological conditions, but there is the possibility of a sampling problem. Clearly volume flow will be determined by the number of vessels. We do observe differences in recordings if uterine vessels away from the placental bed are studied. On the umbilical side, one of two umbilical arteries is being studied. Here we are looking at the influence of the whole umbilical placental bed on the umbilical artery waveform.

Dr. Anderson mentioned the use of a ratio, and of course, a ratio obviates the need to know the angle between the ultrasound beam and the vessel under study. This allows for the use of a simple continuous-wave Doppler ultrasound system. We are not measuring maximum velocity, mean velocity, or volume flow.

In terms of equipment cost, the continuous-wave Doppler unit may be purchased for $3000 to $4000. Cost of the spectrum analyzer is around $12,000 and an ultraviolet paper strip chart recorder retails for $5000 to $8000. Hence, total cost would be some $20,000 to $25,000, which, I believe, could be significantly reduced if machines designed for this specific purpose were manufactured for a large market.

I would now like to answer the specific questions about velocity profiles. We have been analyzing our velocity data on a computer, looking not just at the maximum envelope but also at all of the velocity information beneath that envelope. By an examination of the relationship between maximum and mean velocity it is apparent that the mean velocity waveform follows the maximum velocity waveform over a cardiac cycle. It does seem that flow in the umbilical artery is closer to plug flow rather than parabolic. The umbilical artery is certainly a tortuous vessel spiraling down the cord. This does not influence the waveform significantly, we feel, because the umbilical artery is "locally straight." If we consider the curvature of the umbilical vessels in the cord, then the radius of that curvature is many degrees of magnitude greater than the radius of the umbilical artery itself.

Dr. Mariona asked about the ultrasound energy. We are using a continuous-wave Doppler system of the type that is widely used to record fetal heart activity. The power output from our transducer is 9 mW/cm^2 and less than 10% of this is transmitted to the patient. This is well below the limits of the American Institute of Ultrasound in Medicine.[4]

Dr. Garbaciak raised the question about a group of patients with abnormal uterine and normal umbilical study. In fact such patients are rare. Generally, if the uterine waveform is abnormal then the umbilical study will also be abnormal. We believe that the uterine study may indicate maternal lesion causing fetal effect but the umbilical study indicates fetoplacental effect and will probably prove to be the most important in clinical use.

Finally, Dr. Gant raised a very important question about our data analysis: are we looking here at a self-fulfilling prophecy? Our data have been analyzed in part with respect to time of delivery and is the time of delivery determined by our study results? These Doppler studies have been carried out in conjunction with other studies, in particular, ultrasound growth and fetal heart rate monitoring. It is in fact these latter two investigations that were used for management planning.

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A Circle and the Eight Happinesses

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It has been exactly 10 years since I was last privileged to be your guest speaker. During that decade experience has taught me three things of utmost importance. First, there are only seven ways to project a slide incorrectly. Accordingly, I shall show no slides today. Second, good conversation can be conducted without reference to p values and standard deviations. Therefore my talk will be in the common sense vein, uncluttered by statistics. Third, as a professor, a chairman, and a father, I have learned the fruitlessness of offering good advice. So, be assured there is only encouragement in my presentation.

To begin I should explain that having been invited by your president to make a presentation that expresses a philosophy rather than new scientific techniques, I felt I hardly had the right to refuse. My theme, therefore, is to be woven from two strands. The larger and stronger thread explores our freedom, as obstetricians and gynecologists, to pursue the "Eight Happinesses," which I shall shortly describe. The smaller and brighter thread concerns a special type of circle. My theme opens by referring to this circle in more detail. Allow me to demonstrate.

Tchaikovsky: part of the waltz from
The Sleeping Beauty

What you have just heard is a waltz, and in days gone by the musical signature for a tempo of three beats in a bar was a circle, a sign that signified "perfect time." I shall explain at the end of my talk the relevance of this circle to the eight happinesses. Meanwhile, as we listen occasionally to some further examples of three beats in a bar, may I ask you to notice how varied their presentation can be.

The first two happinesses are Beauty and Truth.

John B. Bogart was the city editor of the *New York*

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Sun. It was he who said that "when a dog bites a man that is not news because it happens so often. But if a man bites a dog that is news."

The logical extension of Bogart's argument is that normality is not remarkable. Thus marriage is not important unless a duke marries a flower girl, and childbirth is not amazing unless it takes place in a taxi.

I do not subscribe to this view. Nevertheless, echoes of Bogart's remark are still heard today in the comments of cynics. Life, they say, is a sexually transmitted disease! But our earthly life is not an inferior example of some abstract heavenly ideal. And should we forget this or grumble that "life is hard," let us ask our selves, "compared to what?" The fact is, life is what we have, and the repetitive miracle of its beauty is a source of wonderment to me more amazing than any illness, any malformation, or any bizarre reports on which the press is founded.

However, the Beauty to which I refer today is not simply the beauty of the female contour, although on this subject I have the natural curiosity of any healthy man. No, the beauty of which I speak is that of the recurring functional normality enjoyed by most women. They are conceived, born, pass through puberty and adolescence, begin to menstruate, and undergo pregnancy. They give birth and lactate, and in due time, via the gateway of the menopause, enter the climacteric. To all these remarkable events we, as obstetricians and gynecologists, are the privileged witnesses. Is it any wonder that colleagues have always found evidence of the Deity as much in the bowl of the pelvis as in the bowl of the heavens?

Now our discipline is unique among clinical subjects in two ways. First, we are privileged to care for women throughout the whole of their lifespan, from conception to death. No other clinical discipline enjoys such a broad opportunity to study the influence of its clinical management on normal human events. Second, we are responsible as much for promoting the health of women as for relieving them from illness. Pediatric gynecology, reproductive physiology, family planning, antenatal care, childbirth, and the passing of the reproductive era are thought of much more today in the positive terms of promoting health than in the negative terms of avoiding disease.

Perhaps as a consequence of these two unique features, in our pursuit of the biologic beauty of a normal reproductive cycle, we are learning to exercise our professional expertise with the minimum of medical interference whenever guidance is sought about the natural episodes of female life. And even when there can be no escape from laboratory inquiry, the physician's bottle, or the surgeon's knife, our unique association with the whole lifespan of woman usually encourages us to plan her management in such a way that the beauty of her normal function is preserved in the next physiologic epoch.

Securing functional beauty requires the concomitant pursuit of truth, and this brings me to the science of our discipline.

"One can't believe in impossible things," said Alice.

"I dare say you haven't had much practice," said the Queen. "When I was your age I always did it for half an hour a day. Why, sometimes I believed as many as six impossible things before breakfast."

In 1984, as we, like Lewis Carroll, peer "through the looking glass," I imagine we no longer find it difficult to believe impossible things. Ten years ago America had already safely transported men across space to the moon. By contrast, no one at that time really foresaw the probability of artificially transporting an egg from the ovary to the uterus, a distance of only 5 cm. Who would have believed that, within the decade, in vitro fertilization was to become so advanced as it is today. Ten years ago we were concerned more with the obstetric problems of newborn babies weighing only 2.5 kg or the advent of active management policies in labor. Today, with flourishing special care baby units, newborn infants weighing 2.5 kg seem to be almost heavyweights. Certainly our present concern is much more for babies weighing 600 to 1000 gm and how we should deliver them.

Similarly, whereas formerly we saw the 36-week infant as being potentially at risk, now at 32 weeks of intrauterine life a child is often thought to be sufficiently well developed to be delivered safely. Indeed, such has been the advance in the care of the young infant that in England today we are encouraging the law to reduce the age of fetal viability from 28 to 26 weeks, possibly even to 24 weeks. Consider also the improvements of ultrasonography over the last 10 years or the obstetric control of the uterus and cervix. Within the decade we have learned to expect extraordinary diagnostic expertise from ultrasound imaging. Also we have learned to relate cervical compliance to uterine effort, so that even under conditions of induced or augmented labor the functional beauty of normal parturition is safely secured for a great many women.

If sometimes we forget or are pessimistic about the scientific advances of our own professional lifetime, we should remember that equal exposure to the obstetric events of only 50 years ago would give us cause for optimism. At that time, women were still grateful for their lives after delivery. However, they soon learned that the march of science was offering them the benefit of health as well as life. Now, quite rightly, they expect maternal satisfaction as well as life and health. Similarly, perinatal progress has shifted the index of satisfactory care from fetal death to infant health and now to the avoidance of long-term handicap. In questions of fetomaternal health we can no longer seek our answers in statistics obtained retrospectively or based solely on the advent of obstetric failure. Instead we must turn our eyes toward the clinical use of prospective trials.

It should not be difficult for us to foresee that in the 10 years ahead there will be many scientific developments concerned with the idea of the fetus as a patient. Some of these possibilities, such as genetic manipulation, are alarming. Some of them, such as intrauterine surgical procedures, are exciting. Some of them, such as the ultrasonic measurement of fetomaternal blood flow, are bewildering.

In all these examples and more, it seems experience repeatedly teaches us two things. First, young people never know enough to be prudent. Therefore they attempt the impossible and achieve it generation after generation. As a result, those of us who are older must increasingly awaken to the fact that our chief goal in education is to create men and women capable of doing new things, not simply of repeating what we or others before us have done. We must encourage independent thinkers, not walking memory banks as indistinguishable from one another as a line of gasoline pumps.

In our pursuit of the beauty of truth, perhaps it is fair to ask, is science truth? The answer is "yes—but only in one form." There are other forms that must be aligned to it (for example, historical, religious, artistic, and moral truths). My point is that the happiness of the truth we pursue in our discipline should be a balance of all these. Only when we have managed to achieve this can we view the long-term effects of our influence with any equanimity.

Lightheartedly, I should say that in my personal pursuit of truth, I always aim to be at least 1 year out of date. In practice, this means that instead of rushing to read each new journal before the ink is dry, I await its appearance in a bound volume. This practice quickly reveals which new advances are of lasting importance and I comfort myself with the thought that if I am only 1 year behind when I retire, on average that is not bad.

Ravel: part of *Bolero*

The next two happinesses are Gentleness and Love.

In my office there hangs a plaque that frames the following words: "This is a department of learning—in which those who pursue wisdom also strive to teach the science of human reproduction, the craft of obstetrics and gynaecology, and the art of feminine understanding."

Now the pursuit of science, to which I have already referred, is all very well, but, as obstetricians and gynecologists, sooner or later we have to do something. And that is where gentleness comes in, for gentleness is of our craft.

How we perform our craft matters a great deal, not only in human terms but also in financial terms. It is interesting to note that perhaps what we are pleased to call "clinical freedom" is, in one sense, no more than a myth. The days have gone when a diagnosis is impossible and treatment is ineffectual. Therefore our professional action today has to be based not merely on our opinion but also on our reasonable evaluation of the state of the art. Failure in this regard provokes the cry of negligence on both sides of the Atlantic. Indeed, I understand[1] that whereas your own liability premiums may be anything from $20,000 to $30,000 per year, we too are concerned about a fourfold increase in our defense premiums, from $52 in 1976 to $253 in 1983. I am not quite sure which side of the Atlantic is sublime and which is ridiculous!

But to return to clinical freedom, there is another sense in which it is not a myth, and that, as this conference manifests, is our freedom to advance medical science and to develop new skills.

Now the gentleness required of new skills is not learned easily. I look back fondly on my own tutor in surgery. "No, no, no, Beazley!" he would shout in frustration, "That's all wrong; get another patient and start again." And then there were the maxims we were taught: "Good surgeons operate with their feet," by which he meant that if pelvic access was difficult from one side of the table, move to the other side. "You can't operate if you can't see!" he would shout, "And if you can see you don't need to be much good at surgery so get on with it."

"If you are assisting," he would say, "try to be like the pouch of Douglas—it holds more than you can, and it's quieter. Meanwhile," he would add, handing me a retractor, "pull on this idiot stick."

Of course, what we were taught in those days was not the theory of operations but the practical craft of surgery—a difference in training I trust we shall continue to maintain. The skill of gentleness is not a skill to be lost simply because today we operate with better anesthetics or deliver babies while the mothers are under epidural analgesia.

But I believe that there was more to the gentleness we were trained to pursue than the simple gentleness of touch. Our great chiefs also taught us the larger gentleness of character and spirit. And naturally enough, it is this that brings me now to the pursuit of the next happiness, which is Love.

It is said that he who works with his hands is a laborer. He who works with his hands and his head is a craftsman. But he who works with his hands, his head, and his heart is an artist. My point is simple. In the discipline of obstetrics and gynecology we all quickly gain experience of the female. However, if we are to understand our patients, what we also need is an acute awareness of femininity. The distinction is not one I could prove to you, and those who perceive no difference between being female and being feminine will charitably discount my point as professorial rambling. Nevertheless, I believe that treating women as feminine rather than just as female results from seeing with the eye of the heart and is the basis of our compassion. It has something to do with that aspect of love without which neither the tongues of men nor of angels amount to very much. Therefore love is an important and ancient happiness that I trust we shall continue to pursue despite the claims of such silly modern extremes as male chauvinism and militant feminism.

Sibelius: part of *Valse Triste*

The fifth and sixth happinesses are Virtue and Devotion.

Drowning a problem in a sea of information is not the same as solving it. And doing things just because they can be done does not justify the doing of them. Yet, is our age not inclined to fall into both these traps? If so virtue and devotion may be happinesses the pursuit of which it is timely for us to reconsider.

Ethics are the principles that govern our actions, and morality is the practice of ethics. In other words, wisdom is knowing what to do next, skill is knowing how to do it, and virtue is doing it. In medical terms, this means that our pursuit of virtue reflects our professional morality.

The Central Association is the largest select body of obstetricians and gynecologists in America. Being select, who here needs to be reminded of the moral dilemmas of our age? Probably no one, for heaven knows, all thinking obstetricians and gynecologists are acutely aware of present moral problems.

Does a child have a right to two parents if this is physiologically possible? How does in vitro fertilization impinge on the concept of the family? Is the word "mother" outmoded? If not, what does it mean? How old is the child who has spent 10 years of embryonic life deep frozen? What are its rights if, meanwhile, its parents die? Do infertile couples have an inalienable right to a child whatever the cost to themselves or society? To what extent is intrauterine surgery justifiable? In both obstetrics and gynecology, has our capacity to interfere outstripped our common sense?

These questions and more confront us on every side. Nevertheless in the last decade, although the president and guests of the Central Association have so clearly addressed themselves to these mounting problems, I understand that as yet no professional philosopher or theologian has spoken here formally on these difficult matters. Probably the same is true of most other great, learned societies, and yet are we quite sure that we have all the answers embodied within the talent of our own organizations?

For example, how many of us recognize that whereas the Hippocratic oath served well for 24 centuries, there have been five major international codes drawn up in the last 40 years? And how familiar are we with the Declaration of Geneva or the Nuremberg Code or the Declarations of Helsinki, Sydney, or Oslo? Yet even these do not deal with organ transplantation, artificial insemination, or in vitro fertilization. In these subjects, not to mention additional complex issues such as the transfer or freezing of embryos or the use of surrogate mothers, do we not need to regularly refresh the broad purpose of our discipline, and can we, as obstetricians and gynecologists, go it alone?

Some might suggest that the marketplace should be the sole determinant of what is to be considered right or wrong in the way of professional action. But surely a profession almost by definition is responsible for upholding its own moral standards. They are not thrust on it from outside.

It is true that answers are beginning to emerge from the slow cogitations of our discipline. It is amazing that only 15 years ago it was thought immoral even to collect eggs and sperm. Today in vitro fertilization is a fact of life, bringing with it both happiness for some childless couples and abuse by some overly enthusiastic practitioners. We appear to have decided also that the origin of life is less practical to pursue than is the age at which a developing embryo should be entitled to the social protection accorded every individual. For the present, that age has been set at 14 days after fertilization.

It is clear that there are many more difficult questions to which answers are needed quickly. And this brings me to my point about the pursuit of the happiness of virtue. It is simply this. In the continuing history of man's struggle to blend together the three great concepts of natural rights, civil rights, and civil liberties, the time is ripe for obstetricians and gynecologists to be playing a major role.

If this view is accepted, it will be understood how important also is our pursuit of the happiness of devotion. If, as a profession, we are to maintain our sense of direction, we must occasionally reappraise what we are devoted to. For example, it seems we still wrangle about the question of medicine for the benefit of the people and medicine for the benefit of the doctors—mutiny over the bounty, as one cynic put it. Clearly we must steadily devóte ourselves to a just compromise of this issue. Also we have to contend with the impact of subspecialization in our discipline and what some people see as an identity crisis. But perhaps we should not be overly troubled by how to define our specialty at different ages.[2] Inevitably we have to be flexible in our approach to health care and, by adapting with good grace to changing circumstances, be prepared to be always seasonable. If, in our long-term devotion to excellence, this necessitates a separation of obstetrics from gynecology, so be it. For now I see only a good many disadvantages in such a radical change. I believe there is a real and continuing need to relate gynecologic therapy to obstetric performance and vice versa. As it stands, our discipline is one that does care for the whole patient. If we increasingly subdivide our specialty, until perhaps we require even professors of fimbriology, we will subvert a long-standing and important principle of our profession.

Whatever answers ultimately emerge to the prickly questions of our day, there is one thing that is sure. It would be wrong for us to be devoted only to modernism. If, in any age, our profession were to be identified solely with being modern, we surely would be doomed because we should quickly lose our identity. To make a pact with permanence, we must be devoted to providing society with something more lasting. It is for this reason that the two happinesses virtue and devotion are best pursued together.

Delibes: part of the waltz from
Coppélia

The last two happinesses are Tolerance and Loyalty.

To be angry you must care about something. And so it is that I find myself partly disagreeing with the pursuit of tolerance. In some areas what we need is more intolerance. Thus, if we love the skills of our discipline, as a profession we must be intolerant of our own clumsiness whenever we find it. Equally, if we seek justice in our profession, we must be intolerant of injustice. And, if in this last comment you sense a clarion call to rise against administrative fog and legislative nonsense, that is no accident. As obstetricians and gynecologists we have done much to bring excellent health care to whole nations—yet those of us who are older have witnessed with mounting frustration an ever-increasing snapping at the heels of our profession by some who spuriously seek to reduce it to a trade or who irresponsibly allege negligence against us. It is not the prerogative of young men to be angry. Many senior and respected clinicians are now shouting "Enough!"

But our intolerance must extend beyond a natural and justifiable irritation at uninformed or irresponsible criticism. We have need to be intolerant of our own professional naivete. And here I refer especially to our approach to the use of high technology. Irrespective of how much of the gross national product should go into health care, two unpalatable facts are shared by both sides of the Atlantic. Costs are rising and resources are finite. Inevitably it follows that technology that is both expensive and complex, so-called high technology, must have restricted availability. In turn this means that, to retain the benefit of high technology at a cost we can afford, there must be some rationing of resources. Therefore is it not somewhat foolish that for a number of years we appear to have responded to many new technical inventions rather like motor enthusiasts being shown an exciting new car? Everyone wants one immediately.[3]

Justifiably this attitude has been criticized, for it has often resulted in the misapplication of high technology. That is to say, distribution has been related more to enthusiastic local fund raising than to any proper scientific evaluation of equipment or its appropriate application.

Today's question, surely, is not whether there should be rationing, but how we should ration; and depending on our different cultural backgrounds, this might be argued according to consumer demand or medically defined needs. In either case the fact remains: We must be more intolerant of grabbing wildly at the latest high-cost technology. With only limited resources available, surely we should be seeking to site high technology, initially, where it can be evaluated prospectively. Thereafter, when its value has been assessed, it can be made more widely available. In the meantime, perhaps we should restrict ourselves more to investigations and therapeutic procedures of proved value, recognizing that when we choose to be involved in the assessment of high technology, a case for research will have to be made. I believe that in the future we shall have to earn our resources. We are no longer born to them, and certainly they will not be thrust on us.[4]

From tolerance, or the lack of it, I pass finally to our pursuit of the happiness of loyalty. Unlike integrity, which we owe to ourselves, loyalty is something we owe to others.

My grandfather, so I am told, was walking me home from primary school one day. Apparently I was crying, having tantrums, and generally being a nuisance. A bossy woman coming the other way remarked to my grandfather, "If that was my child I'd box its ears." "Madam," replied grandfather, "If he was your child I'd box his ears too."

The point is we often put our own affairs in order in a way that includes affection as much as justice. In the case of a profession, affection takes the form of loyalty.

To solve the problems that beset us, our professional loyalty was never more in demand than it is now. Yet what better venue could we find to discuss our anxieties or fire our enthusiasms than our respective colleges and professional associations. And, of these, there is none we hold in higher regard than the Central Association. Our loyalty to its cause, its officers, and its meetings must truly be one of the happinesses we all enjoy pursuing. However, we all realize that in addition, at both the national and local levels, each of us will have to be increasingly involved in the advisory and administrative committees of our colleges, boards, and associations. Indeed, how else are we to solve problems of such immediate personal concern as medical manpower, the control of medical competition, and even the future possibility of medical unemployment.

If these activities sometimes seem tedious, I ask you to remember the bank clerk who was trying to explain to a customer that before his check could be cashed, the back of it must be signed. The customer said, "But I've already signed the front," and left the bank. At the next bank he had the same conversation with another assistant who ultimately, in frustration, picked up a big ledger, leaned over the counter, and banged the customer three times on the head, saying with each blow, "Sign the back." The man did so, and of course his check was then cashed. When he left the bank, who should he meet but the clerk from the first bank, who said, "I see you got your check cashed then. Why wouldn't you sign the back of it when I told you to?" "Ah," said the customer, "You didn't explain it properly." Who knows, with a little vigor correctly applied, we also may be able to persuade people to see things our way. Certainly I believe this is most likely to happen if, as a profession, we loyally support those who fight on our behalf.

Sullivan: part of "Dance a Cachucha,"
The Gondoliers

To close, I should like to tell you of three philosophers who stood around a barrel. On the side of the barrel was written "The essence of life." Each sage in turn dipped in his finger and tasted it. The first sage said that the essence had gone sour. Life was out of step with the past and the only solution was to return to the values of yesterday. The second said the essence had become bitter and nothing could be done but endure life until something better came along tomorrow. The third licked his finger, thought for a moment, and then said, "How sweet." He had learned to accept life as it came, believing that nothing was useless to persons of sense.

Which philosopher shall we resemble? I should like to think it is the third one, openly accepting the difficulties of our times yet, by our approach to them, adapting them to our purpose. And it is here that the circle weaves its way into my story. If composers with only three beats available to them can, as we have heard, give such rhythmic variety to their patterns of notes, surely we, with all the facilities of obstetrics and gynecology at our disposal, can be equally effective in our professional pursuit of the Eight Happinesses.

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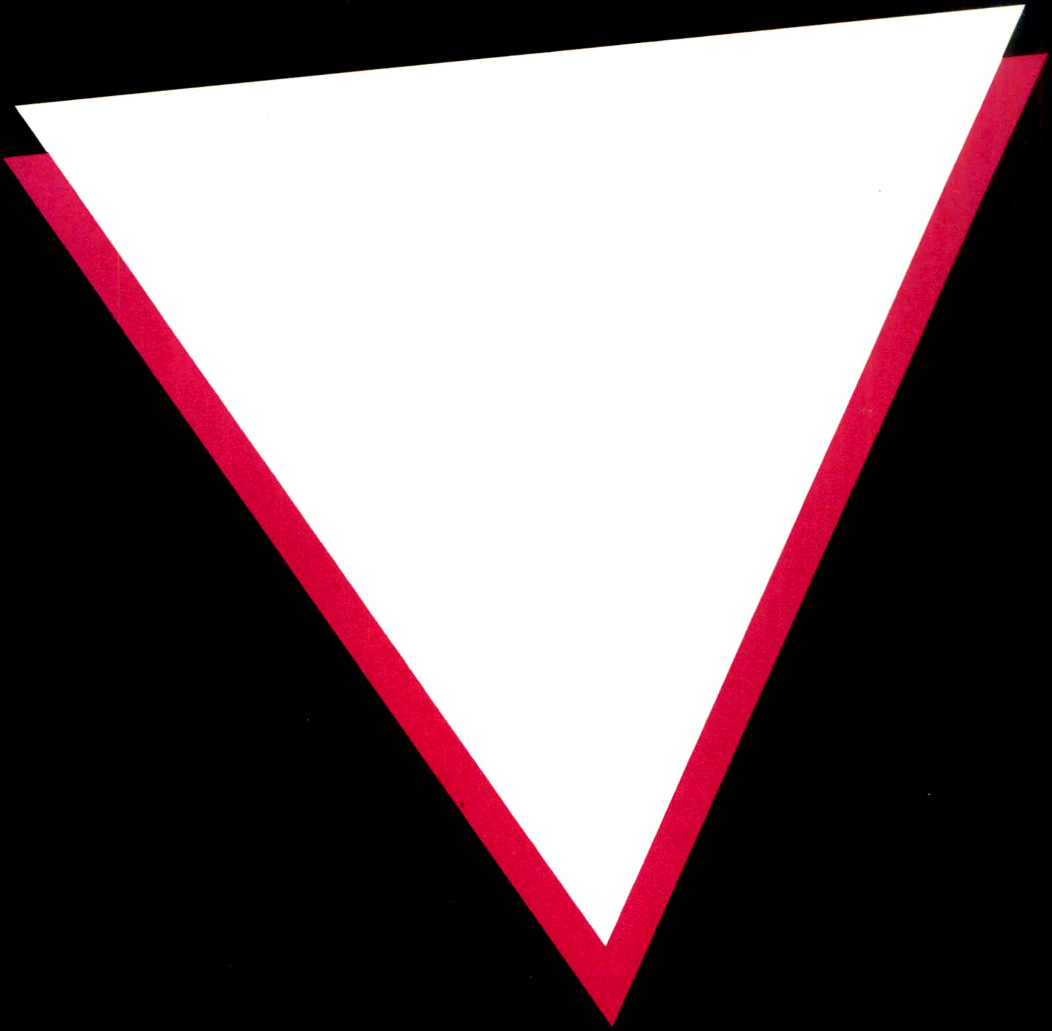

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WARNINGS: Cigarette smoking increases the risk of serious cardiovascular side effects from OC use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use OCs should be strongly advised not to smoke.

The use of OCs is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, liver tumor, gall bladder disease, visual disturbances, fetal abnormalities, and hypertension. Practitioners prescribing OCs should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with OC use is established. One study demonstrated an increased relative risk for fatal venous thromboembolism and several studies demonstrated it for non-fatal venous thromboembolism. They estimate that OC users are 4-11 times more likely than nonusers to develop these diseases without evident cause. One British study reported an excess death rate of 40% in OC users, most of which resulted from cardiovascular disease. Another British study showed a lower death rate in OC users than controls; an increase in cardiovascular deaths was seen but was not statistically significant. A U.S. prospective study failed to disclose increased mortality rates from cardiovascular disorders, but a subset analyzed as a retrospective, case-control study showed significant increases in venous thromboembolism. CEREBROVASCULAR DISORDERS. Two American studies demonstrated an increased relative risk for stroke not shown in prior British studies. In an American study of cerebrovascular disorders in women with and without predisposing causes, relative risk of hemorrhagic stroke was estimated as 2.0 times greater and thrombotic stroke as 4-9.5 times greater in users than nonusers. A British long-term follow-up study reported in 1976 a highly significant association between OC use and stroke. Another study had suggested an association in 1974, but the number of cases was too small to estimate the risk. Subarachnoid hemorrhage has been shown to be increased by OC use in British and American studies. Smoking alone increases incidence of these accidents; smoking and pill use appear to increase risk more than either alone.

MYOCARDIAL INFARCTION (MI). Increased relative risk of MI associated with OC use has been reported. One British study found that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing MI, regardless of OC use. OCs were an additional risk factor. In terms of relative risk, it has been estimated that nonsmoking OC users (smoking is considered a major predisposing condition to MI) are twice as likely to have a fatal MI as nonsmoking nonusers. OC users who are smokers have a 5-fold increased risk of fatal infarction compared to nonsmoking users, and a 10-12-fold increased risk compared to nonsmoking nonusers. The number of cigarettes smoked is important. In determining the importance of these relative risks, baseline rates for various age groups must be considered. (Estimates are based on British vital statistics which show acute MI death rates 2-3 times less than in the U.S. so U.S. death rates could be higher.) Importance of other predisposing conditions in determining relative and absolute risks has not been quantified; other synergistic actions may exist. RISK OF DOSE. Using data from several national adverse reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to estrogen dose in OCs. OCs with 0.1 mg or more of estrogen were associated with a higher risk of thromboembolism than those containing 0.05-0.08 mg but quantity of estrogen may not be the sole factor. This was supported by a U.S. study. A British study found a positive association between dose of progestogen or estrogen and certain thromboembolic conditions. Swedish authorities noted decreased reporting of thromboembolic episodes when higher estrogen preparations were no longer prescribed. Careful epidemiological studies to determine degree of thromboembolic disease risk associated with progestogen-only OCs have not been done. Thromboembolic disease has been reported in women using these products, and they should not be considered free of excess risk. PERSISTENCE OF RISK. Two studies have suggested an increased risk may persist for 6 years after discontinuation of OC use for cerebrovascular disease and 9 years for MI; another study suggested the persistence of risk for subarachnoid hemorrhage. ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES. A large British prospective study estimated mortality rate per 100,000 women per year from circulatory system diseases for OC users and nonusers according to age, smoking habits, and duration of use. The overall annual excess death rate for OC users was estimated to be 20/100,000 (ages 15-34–5/100,000; ages 35-44–33/100,000; ages 45-49–140/100,000). Risk is concentrated in long-term users and in smokers, and may persist after OC discontinuation. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all occurred in women 35 or older. An update provided the following rates: ages 15-34–1/6700 for nonsmokers and 1/2000 for smokers; ages 45 and over–1/2500 for nonsmokers and 1/500 for smokers. Risk appeared to increase with parity, but not with duration of use. Until more women under 35 with continuous use for 5 or more years are available, it is not possible to assess relative risk for this age group. Data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. Estimates include combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease for OCs) plus risk attributable to pregnancy or abortion if the method fails (which varies with the effectiveness of the contraceptive method). The study concluded that mortality associated with all contraceptive methods is below that of childbirth, except for OCs in women over 40 who smoke. (Rates given for pill only/smokers for each age are for smokers as a class. For "heavy" smokers (more than 15 cigarettes a day), the rates would be about double; for "light" smokers (less than 15), about half.) The lowest mortality is with the condom or diaphragm backed up by early abortion. The study also concluded that OC users who smoke, especially over 30, have greater mortality risk than OC users who do not smoke.

Risk of thromboembolic and thrombotic disease associated with OCs increases with age after 30 and, for MI is further increased by hypertension, hyperlipidemias, obesity, diabetes, or history of preeclamptic toxemia, and especially by smoking. The following chart gives a gross estimate of risk of death from circulatory disorders associated with OC use.

SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS–RISK ASSOCIATED WITH USE OF OCs

Age	Below 30	30-39	40+
Heavy smokers	C	B	A
Light smokers	D	C	B
Nonsmokers (no predisposing conditions)	D	C,D	C
Nonsmokers (other predisposing conditions)	C	C,B	B,A

A–Use associated with very high risk.
B–Use associated with high risk.
C–Use associated with moderate risk.
D–Use associated with low risk.

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, discontinue OC immediately. A 4-6 fold increased risk of post-surgery thromboembolic complications has been reported in OC users. If feasible, discontinue OCs at least 4 weeks before surgery associated with increased risk of thromboembolism or prolonged immobilization. Before resuming OC after major surgery or bedrest, balance risks of post-surgery thromboembolic complications with contraceptive needs. Data suggest varicose veins substantially increase risk of superficial venous thrombosis of the leg, the risk depending on the severity of the varicosities. 2. *Ocular Lesions:* Neuro-ocular lesions such as optic neuritis or retinal thrombosis have been associated with OC use. Discontinue OC if there is unexplained, sudden, or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions; and institute appropriate diagnostic and therapeutic measures. 3. *Carcinoma:* Long-term continuous administration of natural or synthetic estrogen in certain animals increases certain tumors, benign or malignant, such as breast, cervix, vagina, uterus, ovary, pituitary and liver. Certain synthetic progestogens, none currently in OCs, increase the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studies reported an increased relative risk (3.1-13.9 times) associating endometrial carcinoma with the prolonged use of estrogens in postmenopausal women. One publication reported the first 30 cases submitted to the registry of cases of adenocarcinoma of the endometrium in women under 40 on OCs. Of the adenocarcinomas found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding when OCs were first given, polycystic ovaries), nearly all occurred in women who had used sequential OCs, which are no longer marketed. No statistical association has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only OCs, although individual cases have been reported. Studies have shown no increased risk of breast cancer to OC or estrogen users. One study found no overall increased risk of breast cancer in OC users but a greater risk was suggested for OC users with documented benign breast disease and for long-term (2-4 years) users. Another study found a history of breast cancer among grandmothers or aunts was significantly more frequent among breast cancer patients who had used an OC continuously for one or more years than among nonusers with breast cancer. One other study indicated an increasing risk of breast cancer in women taking menopausal estrogens, which increased with duration of follow-up. One author suggests that extended (over 6 years) OC use prior to first full term pregnancy was associated with a significant relative risk of breast cancer. A reduced occurrence of benign breast tumors in OC users has been well documented. One study reported malignant melanoma more frequently in OC users than controls and suggests an increased incidence of urinary tract and thyroid cancers. A prospective study of women with cervical dysplasia found an increase in severity and conversion to cancer *in situ* in OC users compared to nonusers. This became statistically significant after 3-4 years of use. Nonreversal of dysplasia within the first 6 months of pill use was suggested to predict progression after prolonged exposure. One study disclosed an increased risk of cancer of the cervix (largely carcinoma *in situ*) in OC users under 40, particularly those who had used OCs over 4 years. There have been other reports of microglandular hyperplasia of the cervix in OC users. One study reported an association between OC use and endocervical adenocarcinoma. In summary, there is no confirmed evidence from human studies of increased risk of cancer associated with OCs. Close clinical surveillance of all OC users is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, take appropriate diagnostic measures to rule out malignancy. Monitor OC users with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms with particular care. 4. *Liver Tumors:* Sudden severe abdominal pain or shock may be due to rupture and hemorrhage of a liver tumor. There have been reports associating benign or malignant liver tumors with short-term and long-term OC use. One study reported use of OCs with high hormonal potency and age over 30 may further increase risk of hepatocellular adenoma. Two studies relate risk with duration of use, risk being much greater after 4 or more years of use. Long-term OC users have an estimated annual incidence of hepatocellular adenoma of 3-4/100,000. Although an uncommon lesion, it should be considered in women presenting with an "acute abdomen". The tumor may cause serious or fatal hemorrhage. Patients with liver tumors have demonstrated variable clinical features which may make preoperative diagnosis difficult. Some cases presented because of right upper quadrant masses, while most had signs and symptoms of acute intraperitoneal hemorrhage. Routine radiological and laboratory studies may not be helpful. Liver scans may show a focal defect. Hepatic arteriography may be useful in diagnosing primary liver neoplasm. 5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring:* Use of female sex hormones–estrogenic and progestational agents–during early pregnancy may seriously damage the offspring. Females exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be of the order of 1/1000 exposures or less. Although there is no evidence that OCs further enhance the risk of developing this type of malignancy, such OC users should be monitored with particular care. A high percentage of women exposed to diethylstilbestrol (30-90%) have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are a precursor of vaginal malignancy. Male children so exposed may develop urogenital tract abnormalities. Although similar data are not available on other estrogens, it cannot be presumed that they would not induce similar changes. Increased risk of congenital anomalies, including heart and limb defects, has been reported following use of sex hormones, including OCs, in pregnancy. One case-control study estimated a 4.7-fold increased relative risk of limb-reduction defects in infants exposed *in utero* to sex hormones (OCs, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some exposures involved only a few days of treatment. Data suggest risk of limb-reduction defects in exposed fetuses is somewhat less than 1/1000 live births. In a large prospective study, cardiovascular defects in children born to women who received female hormones, including OCs, during early pregnancy occurred at 18.2/1000 births, compared to 7.8/1000 for children not so exposed *in utero*. These results are statistically significant. A Welsh study found a statistically significant excess of neural tube defects among offspring of prior OC users (within 3 months) than among controls. The incidence of twin births may be increased for women who conceive shortly after discontinuing OC use. In the past, female sex hormones were used during pregnancy in an attempt to treat threatened or habitual abortion. There is evidence that estrogens are ineffective, and there is no evidence from well controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OCs. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OCs is unknown. If the patient has not adhered to the prescribed schedule, consider possible pregnancy at the first missed period (or 45 days from the last menstrual period if progestogen-only OCs are used) and discontinue OC use until pregnancy has been ruled out. For any patient who has missed two consecutive periods, rule out pregnancy before continuing the OC. If pregnancy is confirmed, tell the patient about potential risks to the fetus and discuss advisability of continuing the pregnancy. Women who discontinue OCs to become pregnant should use an alternate form of contraception for a period of time before attempting to conceive. A 3-month period is supported by a study suggesting increased frequency of neural tube defects in women impregnated during the first 3 months after cessation of OC use. Do not use progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding as a pregnancy test. 6. *Gall Bladder Disease:* Studies report increased risk of gall bladder disease in OC or estrogen users. In one study, an increased risk appeared after 2 years of use and doubled after 4-5 years. In another study, an increased risk was apparent between 6 and 12 months. 7. *Carbohydrate and Lipid Metabolic Effects:* Because a decrease in glucose tolerance has been observed in a significant percentage of patients on OCs, prediabetic and diabetic OC users should be carefully observed. An increase in triglycerides and total phospholipids has been observed in OC users but its clinical significance is unknown. 8. *Elevated Blood Pressure:* An increase in blood pressure has been reported with OC use. Hypertension may occur within a few months of beginning OCs. In the first year of use, incidence of hypertension may be no higher in OC users than in nonusers. Incidence in users increases with exposure and in the fifth year of use is 2.5-3 times that in the first year. Age is strongly correlated with hypertension in OC users. Women with a history of elevated blood pressure (hypertension), preexisting renal disease, history of toxemia or elevated blood pressure during pregnancy, familial tendency to hypertension or its consequences,* or history of excessive weight gain or fluid retention during the menstrual cycle may be more likely to develop elevated blood pressure when given OCs and should be monitored closely. Even though elevated blood pressure may remain within the "normal" range, closely watch elevations, particularly for women with other risk factors for cardiovascular disease or stroke. High blood pressure may or may not persist after OC discontinuation. 9. *Headache:* Discontinue OC and evaluate the cause of onset or exacerbation of migraine or development of a new pattern of headache which is recurrent, persistent, or severe. 10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and missed menses often make users discontinue OCs. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, consider nonfunctional causes. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, use adequate diagnostic measures to rule out pregnancy or malignancy. If pathology has been excluded, time or another formulation may solve the problem. While potentially useful in minimizing menstrual irregularity, change to an OC with a higher estrogen content only if necessary since this may increase the risk of thromboembolic disease. Women with a history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may tend to remain anovulatory or to become amenorrheic after OC discontinuation. Women with these preexisting problems should be advised of this and encouraged to use other contraceptive methods. Post-use anovulation, possibly prolonged, may occur in women without previous irregularities. A higher incidence of galactorrhea and of pituitary tumors (e.g., adenomas) has been associated with amenorrhea in former users compared with nonusers. One study reported a 16-fold increased incidence of pituitary prolactin-secreting tumors among patients with postpill amenorrhea when galactorrhea was present. 11. *Infertility:* There is evidence of impairment of fertility in women discontinuing OCs in comparison with other contraceptive methods, which appears to be independent of duration of use. While impairment diminishes with time, there is an appreciable difference in the results in nulliparous women for OC and other groups 30 months after discontinuation of birth control. For parous women the difference is not apparent 30 months after cessation of contraception. 12. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in OC failure. In progestogen-only OC failures, the ratio of ectopic to intrauterine pregnancies is higher than in nonusers, since the drugs are more effective in preventing intrauterine than ectopic pregnancies. 13. *Breast Feeding:* OCs in the postpartum period may interfere with lactation by decreasing quantity and quality of breast milk. A small fraction of OC hormonal agents has been identified in milk of mothers receiving OCs. Effects, if any, on the breast-fed child have not been determined. If feasible, defer OC use until the infant has been weaned. **Precautions** *GENERAL* 1. Take a complete medical and family history before starting OCs. Pretreatment and periodic physical exams should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant lab tests. As a general rule, OCs should not be prescribed for longer than 1 year without another physical. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may enlarge. 3. Observe patients with a history of psychic depression and discontinue OCs if depression recurs to a serious degree. Patients becoming significantly depressed while taking OCs should stop the OC and use an alternate method of contraception to determine whether the symptom is drug related. 4. OCs may cause some fluid retention. Prescribe with caution, and only with careful monitoring, in patients with conditions that might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma or cardiac, hepatic or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while using OCs. Discontinue OC if jaundice develops. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. OC users may have disturbances in normal tryptophan metabolism that may result in a relative pyridoxine deficiency. The clinical significance is unknown. 8. Serum folate levels may be depressed by OC use. Since the pregnant woman is predisposed to folate deficiency and incidence of folate deficiency increases with increasing gestation, if a woman becomes pregnant shortly after stopping OCs, she may have a greater chance of developing folate deficiency and related complications. 9. Advise the pathologist of OC use when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing OCs. For example: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnandiol excretion. e. Reduced response to metyrapone test. f. Increased phospholipids and triglycerides. g. Temporarily decreased glucose tolerance. 11. Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist and temporary or permanent cessation of wear considered. DRUG INTERACTIONS. OCs may be less effective and there may be increased breakthrough bleeding from interactions with rifampin, isoniazid, ampicillin, tetracycline, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, analgesics, tranquilizers, antimigraine preparations, and antihistamines. OCs may alter effectiveness of such other drugs as oral anticoagulants, anticonvulsants, tricyclic antidepressants, antihypertensive agents (e.g., guanethidine), vitamins, hypoglycemic agents, tranquilizers, hypnotic preparations, and theophylline. *CARCINOGENESIS* See Warnings. *PREGNANCY* Pregnancy category X. See Contraindications and Warnings. *NURSING MOTHERS* See Warnings. **Adverse Reactions** An increased risk of the following serious adverse reactions has been associated with OC use (see Warnings): thrombophlebitis, thrombosis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, mesenteric thrombosis, liver tumors, cerebral hemorrhage, hypertension, gall bladder disease, congenital anomalies, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, Raynaud's disease, arterial thromboembolism. The following adverse reactions have been reported in OC users and are believed to be drug related: bleeding irregularities (breakthrough bleeding, spotting, missed menses during treatment, amenorrhea after treatment), gastrointestinal symptoms, (nausea, vomiting, bloating, abdominal cramps), dysmenorrhea, infertility after discontinuance of treatment, edema, chloasma or melasma which may persist after drug is discontinued, breast changes (tenderness, enlargement, and secretion), intolerance to contact lenses, changes in corneal curvature (steepening), change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution of lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, prolactin-secreting pituitary tumors, chilblains. The following adverse reactions have been reported in OC users and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of hair, erythema multiforme, erythema nodosum, hermorrhagic eruptions, vaginitis, porpyhria, impaired renal function, malignant nephrosclerosis (hemolytic uremic syndrome). **Information for the Patient** (See Patient Package Insert).

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SYNTEX

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Long-term use of intrauterine contraceptive devices in a private practice

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Clinical experience with 1504 insertions of intrauterine contraceptive devices (Lippes Loop, Dalkon Shield, Cu-7) in a private practice is evaluated. Expulsion rates and removal rates for bleeding and/or pain and personal reasons differed for the three types of devices. Pregnancy rates associated with use of the three types of devices were similar. Pelvic inflammatory disease rates were similar for Dalkon Shield and Cu-7 users but were higher than the rate for Lippes Loop users. Use of intrauterine contraceptive devices did not appear to compromise future fertility based on the experience of women who had the devices removed. The study shows that long-term IUD use (up to 5 years) provides a safe and effective method of contraception. (AM J OBSTET GYNECOL 1985;152:169-75.)

Key words: IUDs, pelvic inflammatory disease, contraception

Although it has been more than 20 years since intrauterine contraceptive devices (IUDs) were introduced into clinical practice in the United States, concerns continue to be expressed by physicians and health professionals about the safety of this method of contraception. Ever since their first use in the 1920s, IUDs were suspected of increasing a woman's risk of acquiring pelvic inflammatory disease. However, it was not until 1968 that the first epidemiologic study[1] was published that evaluated the risk of pelvic inflammatory disease in IUD users and users of other contraceptive methods. The rates of pelvic inflammatory disease for IUD, oral contraceptive, and foam users were estimated to be 6.6, 1.3, and 2.5 per 100 woman years, respectively. Since 1968, many studies have reported on the risks of pelvic inflammatory disease in IUD users.[2] These studies also found that IUD users have a higher risk of pelvic inflammatory disease than users of other contraceptive methods. Most studies have found the risks of pelvic inflammatory disease are similar for users of different types of IUDs.

Pregnancy, expulsion, and removal for pain and/or bleeding are accepted complications common to the use of all IUDs. Although improvements have been made in IUD designs since their introduction into clinical practice in the early 1960s, these events still constitute the major reason for IUD discontinuation. In spite of this, IUDs continue to be widely prescribed in the United States and elsewhere. It has been our clinical impression that in our practice IUDs are a safe and acceptable method of contraception. The present study was undertaken to evaluate our experience with the long-term use of different IUDs, the risks of pelvic inflammatory disease, and the fertility of women after discontinuing IUD use.

Material and methods

From December, 1964, to April, 1984, 5375 IUDs (Margulies Spirals, Lippes Loops, Dalkon Shields, Cu-7s) were inserted in women attending our private practice. The type of IUD inserted depended upon the type available at the practice. Four sizes of Lippes Loop (A, B, C, and D) and two sizes of Dalkon Shield (small, standard) were used; 95.4% of the Lippes Loops inserted were size C or D and 74.0% of the Dalkon Shields inserted were the standard size. Usually, only one type of IUD was provided by the practice (Table I). Starting with the first IUD insertion in December, 1964, registration books of all IUD insertions were kept. These books provided basic data on each woman that were used to identify and locate her clinical charts. For each subject, data on her IUD experience and fertility following IUD use were transcribed from her clinical charts onto forms for computer processing. Additional information was obtained from some patients by telephone contact.

The present study was limited to the evaluation of 1504 insertions of Lippes Loops, Dalkon Shields, and Cu-7s (Table I). The number of IUDs inserted represents consecutive insertions, with the exception of Dalkon Shield insertions. The registration books with the information on the Dalkon Shields inserted from April, 1971, to March, 1974, were not available and apparently had been lost. Insertions performed from June, 1973, to April, 1974, were identified by review of financial ledger cards. The registration books and ledger cards provided the only feasible means of identifying IUD users.

From the OB-GYN Associates of Green Bay, Ltd.

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Table I. Number of IUDs inserted

	All IUD insertions		*IUD insertions studied*	
IUD type	*Insertion dates*	*No. inserted*	*Insertion dates*	*No. inserted*
Margulies Spiral	12/64-2/66	230	—	—
Lippes Loop	2/66-8/72	753	4/68- 8/72	499
Dalkon Shield	4/70-6/74	1467	4/70- 6/74	503
Cu-7	3/74-3/84	2925	3/74-10/75	502
Total		5375		1504

Table II. Selected characteristics of subjects at time of IUD insertion

	Type of IUD Inserted		
Characteristic	*Lippes Loop (n = 499) (%)*	*Dalkon Shield (n = 503) (%)*	*Cu-7 (n = 502) (%)*
Age <25 yr	35.5	50.3	52.4
Single	3.8	23.7	33.5
Nulligravid	4.6	22.5	24.7
Nulliparous	5.0	28.7	36.3
Prior abortion	24.4	24.8	34.5
History of sexually transmitted disease	1.8	3.6	2.0
History of pelvic inflammatory disease	2.3	1.4	2.0

All IUDs were inserted according to the manufacturer's directions. Cu-7 users were advised to have the device removed and replaced every 2 or 3 years according to the current use directions. Cu-7 users who had the device removed and replaced by another Cu-7 were evaluated as if they had used only one Cu-7. Women were instructed to return to the clinic if they experienced any problems with the use of the IUD and were requested to return for annual examinations. The rates of loss to follow-up by the end of 5 years were 18.0%, 13.3%, and 24.3% for Lippes Loop, Dalkon Shield and Cu-7 users, respectively. These rates include subjects (Lippes Loop, 7.0.%; Dalkon Shield, 7.8%; Cu-7, 4.4%) who did not return for any follow-up.

The diagnosis of pelvic inflammatory disease was based on the patient's symptoms, physical findings, and laboratory studies suggesting an acute infectious condition of the fallopian tubes and/or the sequelae of such infections, such as pyosalpinx or tuboovarian abscess. The hospital discharge records from the three hospitals (Bellin, St. Mary's, St. Vincent) serving the greater Green Bay area were searched for cases of pelvic inflammatory disease not associated with postoperative or postpartum infections or infections secondary to nongynecologic causes. Thus, for women who remained in the Green Bay area, all cases of pelvic inflammatory disease in IUD users, for which the users were hospitalized, were identified.

IUD-associated events, such as pregnancy, expulsion, and removal, were evaluated by life-table methods[3] that permit evaluation of IUD-related events as a function of the duration of IUD use. Comparisons of these event rates were made by the log-rank statistic.[4] Other comparisons were made with standard statistical tests.[5] Only the significance levels (p values) of these tests are given in the text.

Results

Subjects. Selected characteristics of the subjects are given in Table II. During the time period, there was a trend toward more frequent insertion of IUDs in younger, nulligravid or nulliparous women, especially after the small Dalkon Shield and Cu-7 became available.

IUD event rates. Event rates for Lippes Loop, Dalkon Shield, and Cu-7 users are given in Table III. IUD removals for "other medical" reasons includes pelvic inflammatory disease, menopause, and hysterectomy for uterine prolapse, fibroids, or cervical intraepithelial neoplasia. IUD removals for "other personal" reasons included desire for other methods of contraception and no further need for contraception. Expulsion rates and removal rates for bleeding and/or pain, other medical reasons, planned pregnancy, and other personal reasons, through 5 years of IUD use, were different ($p < 0.05$) for users of the three types of IUDs. All other event rates were similar ($p > 0.10$). Expulsion rates were similar ($p > 0.10$) for Dalkon Shield and Cu-7 users and were lower ($p < 0.05$) for users of these IUDs than for Lippes Loop users. Removal rates for bleeding and/or pain were lowest for Lippes Loop users

Table III. Cumulative gross life-table event rates (per 100 women) after 1, 3, and 5 years of IUD use

	Type of IUD inserted								
	Lippes Loop			*Dalkon Shield*			*Cu-7*		
Event	*1 yr*	*3 yr*	*5 yr*	*1 yr*	*3 yr*	*5 yr*	*1 yr*	*3 yr*	*5 yr*
Pregnancy	3.2	6.4	9.4	3.9	9.8	10.6	2.4	5.6	9.5
Expulsion	7.8	10.1	10.1	1.1	1.6	5.7	1.0	2.5	3.4
Removal									
Bleeding/pain	8.8	18.0	26.8	12.5	34.8	45.5	12.1	27.9	33.4
Other medical	0.7	2.7	4.7	1.5	4.0	10.7	2.7	6.7	9.1
Planned pregnancy	2.8	14.8	18.3	3.6	18.9	23.8	5.6	20.8	28.8
Other personal	1.0	10.5	21.6	4.0	12.7	24.5	3.4	17.0	28.1
Continuation rate	77.5	49.9	35.0	72.6	36.7	21.0	76.1	38.1	25.1

Table IV. Gross cumulative life-table pelvic inflammatory disease rates (per 100 women)

	Duration of IUD use				
Type of IUD inserted	*1 yr*	*2 yr*	*3 yr*	*4 yr*	*5 yr*
Lippes Loop	1.0	2.1	3.0	3.0	3.6
Dalkon Shield	2.6	4.9	5.4	8.9	10.5
Cu-7	3.3	4.6	5.7	7.2	9.5

Table V. Cases of pelvic inflammatory disease

	Lippes Loop ($n = 18$)	*Dalkon Shield* ($n = 34$)	*Cu-7* ($n = 24$)
IUD not removed	9	15	14
IUD removed	9	19	10
Patient hospitalized	2	4	3
Surgical treatment	0	3	3

($p < 0.05$) and highest for Dalkon Shield users ($p < 0.05$). Removals for other medical reasons were similar for Dalkon Shield and Cu-7 users ($p > 0.10$) but were higher than the rate for Lippes Loop users ($p < 0.05$). Removal rates for planned pregnancy were lower ($p < 0.05$) for Lippes Loop users and higher ($p < 0.05$) for Cu-7 users. This probably reflects the higher age and parity of the Lippes Loop users at the time of IUD insertion.

There were two uterine perforations (one per 750 insertions). One perforation probably occurred at the time of IUD insertion. The IUD (a Cu-7) was removed at laparotomy 1 month after insertion. The other perforation (a Lippes Loop) probably occurred after the insertion. Thirty-two months after the insertion the patient became pregnant and had a term delivery. At the time of her 6-week postpartum visit, the IUD string was present in the cervix. X-ray films showed the IUD to be outside of the uterus. The IUD was removed vaginally.

Pelvic inflammatory disease. Rates of pelvic inflammatory disease were similar ($p > 0.10$) for Dalkon Shield and Cu-7 users but were higher ($p < 0.05$) than the rate for Lippes Loop users (Table IV). Overall, there were 76 cases of pelvic inflammatory disease (Table V). Most of the cases were mild and were treated by IUD removal and antibiotics or antibiotics only. Taking into consideration all cases of pelvic inflammatory disease, the rates (per 100 woman years of IUD use) were Lippes Loop, 1.0; Dalkon Shield, 2.3; Cu-7, 2.0.

Pregnancy outcomes. For pregnancies that occurred with IUDs in situ there were no differences ($p > 0.10$) in their outcomes according to the type of IUD used (Table VI). Among women who became pregnant with an IUD in situ and who did not have an elective abortion, 53.6% of those who retained the IUD spontaneously aborted compared to 15.9% of those who either expelled the IUD or had it removed.

One hundred ninety-seven women had the IUD removed for planned pregnancy. Ten women changed their minds and continued to contracept after the IUD was removed. Pregnancy outcomes were known for 95% of the remaining 187 women. The outcomes were similar ($p > 0.10$) for users of the three IUD types. There were no ectopic pregnancies and 90.6% of the women who became pregnant had term deliveries. Of special interest were the pregnancy outcomes of women who had pelvic inflammatory disease while using an IUD. Table VI gives a breakdown of the pregnancy intentions of these women. Most women (54%) did not want additional children and continued to contracept. Among 12 women who wished to become pregnant and who had known pregnancy outcomes, seven had term deliveries.

Comment

Since 1964, we have inserted 200 to 300 IUDs (Margulies Spiral, Lippes Loop, Dalkon Shield, and Cu-7) per year in our private practice. This rate remained constant over time. The type of IUD used depended on availability and physician preference.

Although it is recognized that pelvic inflammatory

Table VI. Outcomes of pregnancies

	Pregnancy with IUD in situ						*Pregnancy after IUD removed for planned pregnancy*					
	Lippes Loop (n = 36)		*Dalkon Shield (n = 36)*		*Cu-7 (n = 23)*		*Lippes Loop (n = 55)*		*Dalkon Shield (n = 63)*		*Cu-7 (n = 69)*	
Outcome	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
No information after IUD removal*	–	–	–	–	–	–	2	–	5	–	2	–
No pregnancy*	–	–	–	–	–	–	0	–	1	–	5	–
Surgically sterile*	–	–	–	–	–	–	1	–	–	–	–	–
Pregnant, outcome unknown*	3	–	1	–	–	–	–	–	–	–	1	–
Elective abortion†	5	15.2	12	34.3	8	34.5	2	3.8	0	0.0	2	3.3
Ectopic pregnancy†	4	12.1	3	8.6	1	4.3	0	0.0	0	0.0	0	0.0
Spontaneous abortion‡	9	32.1	10	43.4	5	33.3	5	10.0	3	5.2	1	1.7
Premature delivery‡	1	3.6	1	4.3	0	0.0	1	2.0	1	1.8	1	1.7
Term delivery‡	14	50.0	9	39.1	9	60.0	44	88.0	53	93.0	57	96.6

*Excluded from calculations of percentages.
†Percent based on all pregnancies with known outcomes
‡Percent based on all pregnancies with known outcomes excluding elective abortions.

Table VII. Pregnancy following pelvic inflammatory disease

A. Pregnancy not desired		45
Continued contraception		
IUD not removed	7	
IUD removed	7	
Oral contraception	9	
Tubal ligation	15	
Vasectomy	2	
Partner sterile	1	
Abortion	1	
Menopause	3	
B. Pregnancy desired		12
Term delivery	7	
Spontaneous abortion	1	
No pregnancy within 1 yr	2	
No follow-up	2	
C. Pregnancy desire unknown		12
D. Surgically infertile		7
Related to pelvic inflammatory disease	2	
Unrelated to pelvic inflammatory disease	5	
Total		76

disease may occur in IUD users, the data presented in this paper suggest that women who use IUDs may not be at any higher risk of pelvic inflammatory disease than nonusers of IUDs. A pelvic inflammatory disease rate of about 2% per year in the general population is consistent with the rate in the present study for women who used the Dalkon Shield and Cu-7. Lippes Loop users had a significantly lower rate of pelvic inflammatory disease. The only apparent explanation for this is that a higher proportion of the Dalkon Shield and Cu-7 users were among those generally thought to be at a higher risk of exposure to sexually transmitted diseases and pelvic inflammatory disease, namely, single, nulligravid or nulliparous women. The results of the study do not support the contention of Tatum et al.[6] that the risk of pelvic inflammatory disease in Dalkon Shield users may be increased because of the ability of bacteria to enter the interfilamental spaces of the tail string. Also, the finding of the case-control study reported on by Lee et al.[7] that Dalkon Shield users have a risk of pelvic inflammatory disease that is more than five times higher than that of users of other types of IUDs is inconsistent with the results of the present study.

The results of the present study are reassuring in terms of the outcomes of pregnancies in women who had the IUD removed to become pregnant. Among 170 conceptions there were no ectopic pregnancies and more than 90% of the women had term deliveries. These results suggest that IUD use neither impairs future fertility nor affects the outcomes of future pregnancies. If the use of IUDs were to cause nonreversible changes to the tubal epithelium because of clinical and subclinical tubal infections in a significant proportion of the IUD users, this would become immediately apparent in any follow-up study of pregnancies conceived after IUD use. In the patient population evaluated, involuntary infertility following IUD use was minimal.

The use of IUDs has been a very economical, safe, and effective method of contraception for many women attending our practice. Although some clinicians do not advocate the use of IUDs for nulliparous women since their use may impair future fertility, on the basis of our experience with our patient population, we continue to recommend the use of IUDs for this patient group. The data reviewed in this report provide reassurance that long-term IUD use (up to 5 years) continues to provide a safe and effective method of contraception with low rates of serious complications.

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Discussion

DR. WALTER G. SAUNDERS, Sheridan, Wyoming. In their article Drs. Sandmire and Cavanaugh noted a pelvic inflammatory disease rate for three separate types of IUDs similar to that expected in the general population. Similarly the pelvic inflammatory disease rates for Dalkon Shields were far lower than those in previous studies.[1, 2] A recent report from Britain[3] did not compare IUD users to non–IUD users but found no statistically significant difference among infection rates in users of Lippes Loops, Cu-7s, and Dalkon Shields, which corroborates the authors' study. In other respects (continuance rates, uterine perforations, ectopic pregnancies, etc.), the data obtained in this paper are similar to those in previously published reports. Following removal of an IUD, pregnancies in women who had not had pelvic inflammatory disease went well. The complications of conceptions with in situ devices paralleled results of others and would, I believe, be quite similar to those from my practice. In my opinion the number of conceptions after pelvic inflammatory disease was too small to be meaningful.

I do not want to become embroiled in a comparison of papers with disparate data, but the question remains what can be gleaned from this study to alter practice patterns and educate patients considering two decades of IUD insertion experience in this country. I would like to stimulate discussion from the author and others in the audience by asking several questions. Dr. Sandmire, in this article you and your associates have treated a number of cases of pelvic inflammatory disease without removing the IUDs. Would you comment historically and currently on this practice in view of the current Dalkon Shield litigation and also in terms of your experiences today? Do you now routinely remove IUDs when you suspect a pelvic infection? Second, do you think that pelvic inflammatory disease has changed since the late 1960s? Do you use the same criteria for diagnosing pelvic inflammatory disease as you did in the earlier phases of this study or have you changed your criteria? Therefore, do you think, in the late 1960s and early 1970s, we were underdiagnosing subtle pelvic inflammatory disease in large numbers of IUD users? Since the Dalkon Shield has been relegated to the medical junk heap and the medical-legal gold mine, the data obtained in this study regarding the Shield must fall under the heading of "too little, too late."

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DR. LEE B. STEVENSON, Southfield, Michigan. Dr. Sandmire's evaluation, made possible by the registration logs in his office, was apparently uncompromised by the loss of some books (April, 1971, to March, 1974). This loss could spell disaster, however, if all Dalkon Shield users must be identified or contacted.

The low incidence of pelvic inflammatory disease in this series is outstanding. Only seven patients required admission to the hospital. About half of those had surgical management. Does Dr. Sandmire credit this low incidence to the features of the clean-living, rural population of Green Bay?

The increased pelvic inflammatory disease rates for Cu-7 users probably mirror the differences in time and life-styles for these "modern" people. Changes in patterns of IUD use parallel the changes in our times and social attitudes. For example, one should expect more Cu-7 users than Lippes Loop users to request removal for bleeding and/or pain because this reflects the differences described in this group of younger, single, nulligravid or nulliparous women. Conversely removal of Lippes Loops for planned pregnancy was less in the group of older, married, parous, "sedate" women.

It is pleasant to agree that the history of pelvic inflammatory disease is not a contraindication to the use of an IUD. Fertility after IUD removal was quite acceptable. Was there a difference in observed fertility after longer years of use beyond what could be expected from the advanced age of the women? Where fertility was compromised, was it "proved" before IUD use?

No Lippes Loops were expelled after 3 years of use but expulsion of Dalkon Shields and Cu-7s continued after 3 years. How do you manage expulsion of an IUD? Do you insert another IUD? Do you have a limit on reinsertions per patient?

Permanent sterilization is a desirable alternative after (or before) removal of an IUD. It is one of the choices the Cu-7 user should consider at least every 3 years.

Now back to the Dalkon Shield that was taken off the market (and discontinued by the authors) in 1974. The August, 1983, *FDA Drug Bulletin* recommends: "Due to an increased risk of pelvic inflammatory disease (PID), the Dalkon Shield intrauterine device (IUD) should be removed from any woman still wearing one. Women wearing the Dalkon Shield have a five-fold increased risk of PID compared with women using other types of IUD's."

Do you feel any anxiety for your patients who continue to depend on a Dalkon Shield? Have you had any malpractice suits involving an IUD? We should be more aggressive in removing Dalkon Shields.

To paraphrase a ballad to make a point:

Take it out, take it out, cried the voice from the womb,
Take it out, take it out; keep away from the tomb.
But for author Sandmire, even with figures fine,
Shields left in place can haunt him in time!

Do not forget that deaths associated with the use of IUDs have been reported. "Doctors should remember when managing sick women that deaths may occasionally be associated with intrauterine contraceptive devices"[1] warn our British colleagues.

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DR. JOHN L. DUHRING, Toledo, Ohio. I just want to give my opinion of IUDs. In the month of June, 1975, two of my patients, one with a Saf-T-Coil, one with a Lippes Loop, developed gram-negative septic shock. Fourteen blood cultures in these two women, eight for one and six for the other, all grew out *Pseudomonas* and *Escherichia coli.*

All you need is one such patient. I have had two. I do not use IUDs.

DR. PEDRO A. POMA, Melrose Park, Illinois. Although not as serious as the other problems, imbedded and "lost" IUDs are very annoying to patients and physicians alike. I wonder how the authors deal with this problem.

DR. FIROOZ BANOONI, Southfield, Michigan. With all the publications that have recently stemmed from the use of IUDs in nulligravid women versus multigravid women, I wonder whether we should still use them in nulligravid women, although Dr. Sandmire says there is no difference. How many physicians are using IUDs as frequently in the nulligravid women as in the multigravid ones? What would be the answer to the nulligravid patients for whom you recommend an IUD, and then she says, "Oh, I went to two other doctors that told me you shouldn't be using them," or they come back and say I should remove it because they told me it should not be used.

Is there any difference in incidence of pelvic inflammatory disease between urban, indigent patients with IUDs and in private practice patients who have IUDs?

Were Dr. Sandmire's patients primarily private patients or clinic patients?

DR. EDUARD EICHNER, Cleveland, Ohio. On the question of the bad results with the Cu-7, I was in the early study group of the Cu-7 with the Loop and others. I am wondering whether some of the bad results are due to the fact that the Cu-7 is now being used as a contraceptive in the patient who is not under control. In other words, "I did nothing, and therefore, I come to have the Cu-7 inserted as an emergency contraceptive." I wonder whether that type of patient, who is not careful of what she is doing, is one who develops pelvic inflammatory disease.

DR. SANDMIRE (Closing). Dr. Saunders asked a couple of questions, and one was whether we removed the IUD in patients with pelvic inflammatory disease. We removed the IUD in the patient who had signs and symptoms of a serious infection. For the patient who can be treated on an ambulatory basis, we will wait 2 or 3 days before deciding whether to remove the IUD. In other words, we start treatment and see her in 2 or 3 days. If she is not substantially improved, then we will remove the IUD. There is some evidence in the literature that this is not necessary, that the results of treatment will not be favorably influenced by removing the IUD. In our experience I see that exactly half of patients with pelvic inflammatory disease had the IUD removed during treatment.

I do not think we have changed our criteria for the diagnosis of pelvic inflammatory disease during the years of the study. Basically, if the physician treated the patient with antibiotics after making a diagnosis of pelvic inflammatory disease, then that patient satisfied the requirements for our study. We think this would be the same and not biased in any way according to what type of IUD the patient had.

Dr. Saunders suggests that our findings are "too little, too late," as they relate to the medical-legal questions associated with Dalkon Shield usage. He is partially correct; however, there are still 3000 pending claims relating to the Shield. In addition, our findings are in agreement with a large British Study[1] published after we had submitted our abstract and involving 13,000 patients. Their cohort study also indicated no higher incidence of pelvic inflammatory disease in Shield users compared to Lippes Loop and Cu-7 users. The study cited by Dr. Stevenson from the *FDA Bulletin* is an article authored by Lee and is a case-control study. It is not a cohort study, and there are certain shortcomings in case-control studies not present in cohort studies. I think it is a mistake that people have been misled on the basis of that one study since all other studies have found no significant difference in infection rate between different kinds of IUDs.

Dr. Stevenson asked whether we credit the low incidence of pelvic inflammatory disease in our series to a clean-living and rural population group. The answer for the Lippes Loop is yes, but our incidence of infection for Cu-7 and Shield users was not all that low, and I think that the social activities that influence infection rates changed in the 1970s. Most of our Lippes Loop devices were inserted in the late 1960s.

What about the nulliparous woman who has asked for an IUD? Not all nulliparous patients are suitable for an IUD. If she has a stable relationship, she has only one sex partner, and her sex partner has only her as a sex partner, then she may be a suitable candidate after very careful warning that the incidence of infection may be greater in IUD users that in nonusers. The increased risk relates primarily to being exposed to germs which cause the infection.

As far as Dr. Duhring is concerned, I do not think two cases is a very big series. I am sorry, but it just is not.

As far as Dr. Stevenson's other question, was there a difference in observed fertility after a longer period of IUD use, there were so few patients who did not achieve pregnancy after IUD removal that we did not assess whether those patients had an IUD in place for a longer period. It was just an insignificant number. I think there were only seven of 197 patients who had the IUD removed for planned pregnancy who did not succeed.

The other question of Dr. Stevenson was, in those who failed to become pregnant, did they have proved fertility before the IUD was inserted. That is a very good question. The answer is I do not know. They did not have proved fertility. I do not know that they were infertile either, and I would not make any inference in that direction.

How do we manage expulsion? If the patient wants the IUD replaced, we put it back in. If she wants it replaced a third time, we put it back in. We explain the options, and it is really up to her. She makes the decision on how she perceives the other options available for contraception.

Do we have anxiety for patients who continue to depend on the Dalkon Shield? This is an important problem for perhaps all of you. How can you find those patients? Most of you probably do not have a registration book relating to IUD insertions. If you went from a billing system to a computer system and your hard-copy ledger cards have not been retained, there is no way you are going to find those patients.

Do I have anxiety for those patients as far as their health? No. Do I have legal anxiety for myself? Yes.

Have I had any malpractice suits in association with an IUD? Yes. One patient had a pelvic abscess, and I told her we would try to drain it through the vagina. If we did not succeed, we would have to perform a pelvic laparotomy and possibly total abdominal hysterectomy and bilateral salpingo-oophorectomy. She said to me, in front of the nurse, "Well, if you don't have to take everything out and you just drain it through the vagina, can you do a tubal ligation at the same time?" I said, "No, because of the infection we wouldn't do any additional elective procedure like that." We were not able to drain it through the vagina. We removed the reproductive organs, and 3 years later, just before the statute ran out, she sued me along with A. H. Robins Company because I "deprived her of her fertility."

She cannot get a doctor to testify, but in Wisconsin the compensation panel chairman is obliged to find some doctor as an independent arm of the court to testify. Well, maybe they won't find anybody willing to assert negligence, but we can get dragged in on IUD suits in which patients are suing the company.

A member from the audience asked what do we do about missing IUDs. They must be found. IUDs that are missing must be found, and during a pregnancy termination, if the IUD is not retrieved, you must look for it. If you do not find an IUD in the uterus, then obtain an x-ray film of the entire abdomen and pelvis. Do not depend on ultrasound. You will miss some IUDs when searching for them by ultrasound. Now, sometimes someone will say, "Well, if you can do it by ultrasound, maybe you can tell whether it is in the wall or outside the uterus better than with a flat plate." There is nothing better than an anteroposterior and a lateral hysterosalpingogram to find out exactly where that IUD is, but most of the time it is not there at all. The patient has had an unnoticed expulsion. It must be determined that all missing IUDs are no longer in the patient's body.

In terms of socioeconomic situation, I think I covered that.

The nulliparous woman who has multiple sexual partners and/or whose partner has multiple partners is not a candidate for an IUD. That is also true for multiparous women, but it is more important for the nulliparous patient who may have her still unused fertility interrupted because of an infection. I think that also answers Dr. Eichner's question.

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The midforceps: Maternal and neonatal outcomes

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A retrospective review of midforceps deliveries occurring between 1976 and 1982 at a county teaching hospital is presented. Midforceps deliveries were performed in 0.8% of deliveries (176 of 21,414) during this period, a rate reflecting the general admonition against potentially traumatic injury to the infant. Under these conditions, midforceps deliveries were associated with active and second-stage labor abnormalities, abnormal fetal heart rate patterns, maternal perineal lacerations, low 1-minute Apgar scores, and neonatal cephalohematomas more frequently than were deliveries of the remainder of the patients. Epidural anesthesia was significantly associated with midforceps deliveries. Midforceps patients were matched to similar groups who were delivered by cesarean section or low forceps or who had spontaneous births. The findings do not document an increase in short-term neonatal morbidity in the midforceps group under the conditions described. (AM J OBSTET GYNECOL 1985;152:176-83.)

Key words: Midforceps, neonatal morbidity, neonatal outcome, maternal morbidity

During the past 25 years, as maternal and neonatal mortality rates have declined, attention has been directed to improving infant morbidity. Procedures associated with risk of long-term infant morbidity such as internal podalic version, breech extraction, high forceps, and "difficult" midforceps deliveries have generally been abandoned in favor of cesarean section with less risk of fetal injury. These concerns about infant outcome have been largely responsible for the threefold rise in the cesarean section rate between 1970 and 1978.[1] Yet, while podalic version, breech extraction, and use of high forceps are rare today, midforceps deliveries are still relatively common in some obstetric services. The rationale for their use is that the "difficult" midforceps operations are avoided by the good judgment of the experienced clinician. The veracity of the above argument has been questioned recently by Cyr et al.[2] and earlier by Chiswick and James[3] and Friedman.[4]

The present study was undertaken to evaluate maternal and infant outcomes in a population in which midforceps deliveries were used infrequently. During this time period potentially difficult vaginal deliveries were managed with the use of oxytocin with spontaneous vaginal delivery, low forceps delivery, or cesarean section, or less commonly, with midforceps. Our hypothesis was that the conservative use of midforceps was not associated with increased neonatal morbidity and was associated with acceptable maternal morbidity.

Material and methods

The study population consisted of infants delivered in the obstetric service at Cleveland Metropolitan General Hospital from July 1, 1976, through 1982. Antepartum, intrapartum, and neonatal data for all patients were collected and entered prospectively into a computer data base file during the pregnancy and neonatal period. A midforceps delivery was defined traditionally as one in which the fetal vertex was engaged in the pelvis and above the perineum. All rotations were classified as midforceps deliveries. The hospital chart on each patient identified as being delivered by midforceps was reviewed to confirm that the procedure was a midforceps delivery, to document maternal morbidity, to confirm fetal heart rate findings, and to add data missing from some files such as duration of epidural anesthesia or the need for forceps rotation. Infants with major congenital anomalies and stillbirths were excluded.

Labor graphs were plotted for each patient and entered into the computer data base at the time of each delivery. Labor abnormalities were identified as described by Friedman[4] with the use of cervical dilatation and station of the presenting part plotted against time. Maternal trauma was defined in terms of cervical and perineal lacerations and estimated blood loss exceeding 500 ml at delivery.

Additional intrapartum fetal risk factors were de-

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Table I. Labor abnormalities in the midforceps delivery group and other patients

	Midforceps patients (n = 176)		*All patients (n = 21,238)*		
Labor abnormalities	*n*	*%*	*n*	*%*	*p value*
Prolonged latent phase	3	2	494	2	NS
Protraction, active	57	32	5343	25	<0.03
Arrest, active	20	11	1070	5	<0.0002
Protraction of descent	43	24	769	4	<0.00001
Arrest of descent	53	30	540	3	<0.00001
Second stage >2.5 hr	33	19	335	2	<0.00001

Table II. Characteristics of the study population

	Midforceps patients		*All patients*		
	n	*%*	*n*	*%*	*p value*
Nulliparity	141	80	9704	45	<0.00001
Birth weight >4000 gm	8	5	1123	5	NS
Large for gestational age (>90th percentile)	26	15	2432	11	NS

fined as oxytocin augmentation of labor, the need for fetal monitoring, the presence of thick meconium-stained amniotic fluid, and fetal heart rate patterns suggesting fetal distress. The need for fetal micro–blood determination was evaluated, as was evidence of excessive birth weight. Neonatal charts were reviewed when indicated to confirm neonatal injuries such as neonatal seizures, central nervous system bleeding, and seventh nerve or brachial nerve palsies.

The study population of midforceps deliveries was then compared to the remainder of the population delivered during the same period. The data for this control population were also collected and entered into the data base at the time of delivery. The individual charts of the control patients were not reviewed.

In order to determine the effects of the midforceps procedure when controlling for risk factors, the midforceps delivery group was then compared to similar groups matched by gestational age, birth weight, labor abnormality, and fetal heart rate abnormality and delivered by low forceps, by cesarean section, or spontaneously. The outcome measures between the groups were compared using the χ^2 statistic.

Results

The incidence of midforceps deliveries was 0.8% (176 of 21,414 deliveries). The incidence of primary cesarean section during this period was 9.3%. Labor abnormalities are listed in Table I. Prolonged latent phase was not different in the two groups. Active-phase and second-stage abnormalities were much more common in the midforceps group.

Table III. Intrapartum factors in the midforceps delivery group and other patients

	Midforceps patients		*All patients*		
Intrapartum factors	*n*	*%*	*n*	*%*	*p value*
Oxytocin augmentation	68	39	3539	17	<0.00001
Epidural anesthesia	89	51	4259	20	<0.00001
Fetal heart rate abnormalities	61	35	1369	6	<0.00001
Scalp pH obtained	40	23	852	4	<0.00001
Scalp pH <7.25	17	10	216	1	<0.00001
Meconium (thick)	28	16	2095	10	<0.008

Characteristics of the study populations are given in Table II. Nulliparity was much more frequent in the midforceps delivery group than in the general population. Infants of excessive size, defined as either being large for gestational age or weighing >4000 gm, were not significantly more common in the midforceps group.

Intrapartum factors that may be related to fetal outcome are presented in Table III. The increased incidence in the use of oxytocin to augment labor was expected in this risk group. Epidural analgesia was associated with 51% of the midforceps delivery group, which was much higher than for the control population (20%). Fetal heart rate patterns suggestive of fetal distress were observed in about one third of the midforceps cases. Bradycardia was present in 14%, late decelerations in 5%, and severe variable decelerations in 16% of midforceps deliveries. Fetal micro–blood sampling was performed in 23% of cases, with fetal pH <7.25 in 10% of the midforceps group. Umbilical cord pH values were not obtained.

Maternal morbidity was expressed in terms of soft tissue injury and blood loss. These data are presented in Table IV. It is evident that third-degree perineal lacerations, many with rectal mucosal extension, occurred in nearly half of the midforceps deliveries. Blood loss estimated to be >500 ml occurred in 22% of the midforceps delivery group.

Short-term neonatal outcomes are presented in Table

Table IV. Maternal short-term morbidity in the midforceps delivery group and other patients

	Midforceps patients		*All patients*		
Maternal morbidity	*n*	%	*n*	%	*p value*
Cervical laceration	21	12	786	4	<0.00001
Third-degree laceration	80	46	1510	7	<0.00001
Estimated blood loss >500 ml	39	22	1993	9	<0.00001

Table V. Short-term neonatal morbidity in the midforceps delivery group and other patients

	Midforceps patients		*All patients*		
Neonatal morbidity	*n*	%	*n*	%	*p value*
1-min Apgar score <7	57	32	3729	18	<0.00001
5-min Apgar score <7	7	4	769	4	NS
Cephalohematoma	13	7	318	1	<0.00001
Seizures	2	1	210	1	NS
Shoulder dystocia	4	2	222	1	NS
Brachial palsy	2	1	107	1	NS
Seventh nerve palsy	2	1	109	1	NS

V. Depressed 1-minute Apgar scores and cephalohematomas occurred more frequently in the midforceps delivery group. The rest of the indicators of short-term fetal morbidity were not increased. There were no skull fractures.

Fetal distress was the immediate indication for delivery in 65 midforceps cases (37%), and dystocia was the indication in 66 cases (38%). When the midforceps cases that were performed primarily for either dystocia or fetal distress were compared to matched cesarean section cases, the only significant difference in short-term outcome was the higher incidence of low 5-minute Apgar scores in the cesarean section group (Table VI). The distribution of cephalohematomas according to the indication for delivery was not significantly different.

The level of training of the most senior physician attending the delivery is listed in Table VII, along with the distribution of cephalohematomas. The presence of forceps rotation, nearly all cases of which were from at least the occiput transverse position, is indicated in Table VIII, along with the distribution of cephalohematomas.

The midforceps delivery group was then compared to the matched groups delivered by low forceps, by cesarean section, or with spontaneous birth (Table IX). There were no significant differences in third-degree perineal lacerations between midforceps deliveries and matched low forceps deliveries. Low 1-minute Apgar scores were more frequent in the midforceps group ($P < 0.05$). Shoulder dystocia, seventh nerve palsies, brachial paralysis, neonatal seizures, and central nervous system hemorrhage were not significantly different in the groups indicated.

Comment

Many of our more recent fetal surveillance techniques such as antepartum and intrapartum fetal monitoring, fetal micro–blood analysis, and the liberal use of cesarean section for dystocia are all directed toward minimizing the risk of either hypoxic or traumatic fetal injury. The result of much of this concern has been a dramatic increase in the cesarean section rate, the major increases resulting from dystocia, breech presentation, and repeat cesarean section.[1]

Recently Cyr et al.[2] reported both a fourfold increase in the cesarean section rate (5% to 19%) and a threefold rise in midforceps deliveries (5% to 15%) over an 18-year period. These changes in delivery technique occurred during both the development of electronic fetal monitoring and the emergence of epidural anesthesia as a technique commonly used during labor. It was the authors' impression that the frequent use of midforceps was associated with a significant increase in traumatic birth injuries to the infant which were unrelated to the skill of the operator.

This study provides insight into the maternal and infant outcomes of an obstetric service in which difficult midforceps deliveries were not encouraged, as exemplified by the 0.8% midforceps delivery rate. It is possible that some deliveries classified as low forceps deliveries may have in fact been midforceps deliveries, thus the actual midforceps rate could be somewhat higher. Review of 100 low forceps cases showed 5% were misclassified and were apparently midforceps. The low forceps rate at our institution during the same years was 7.1%, and the primary cesarean section rate was 9.3%.

From our data it is clear that midforceps deliveries were more commonly associated with active-phase and second-stage dystocia and were associated with a higher risk of cervical and third-degree perineal lacerations and excessive maternal bleeding at delivery than the general population. Fetal heart rate patterns suggesting fetal distress were often associated with midforceps deliveries. Only 10% of the midforceps group was found

Table VI. Comparison of midforceps delivery cases performed primarily for either dystocia or fetal distress with matched cesarean section patients

	Midforceps delivery patients				*Cesarean section patients*			
	Fetal distress (n = 65)		*Dystocia (n = 66)*		*Fetal distress (n = 65)*		*Dystocia (n = 66)*	
	n	%	*n*	%	*n*	%	*n*	%
1-min Apgar score <7	23	35	12	18	32	49	17	26
5-min Apgar score <7	3	5*	1	2	12	18*	1	2
Cephalohematoma	4	6	6	9	1	2	3	5
Shoulder dystocia	1	2	3	5	0		0	
Brachial plexus injury	0		2	3	0		0	
Seventh nerve palsy	0		0		0		0	

$^*p < 0.02$.

Table VII. Distribution of midforceps deliveries and associated hematomas with level of physician training

Physician level	*Midforceps delivery (%)*	*Cephalohematoma*	
		n	%
First year	1	1	8
Second year	27	2	15
Third year	20	4	31
Fourth year	23	5	38
Faculty	26	1	8

Table VIII. Association of midforceps rotations with cephalohematomas

	Midforceps rotation		*Cephalohematoma*	
	n	%	*n*	%
Yes	68	39	5	38
No	104	59	8	62
Not recorded	4	2		

to be preacidotic or acidotic before delivery. It may be more prudent to evaluate second-stage heart rate decelerations more objectively by means of scalp pH as a more reliable indicator of fetal distress than to resort to midforceps delivery because of worrisome heart rate patterns.

The increased incidence of maternal perineal and cervical lacerations with midforceps delivery must be balanced against potentially more serious sequelae associated with cesarean birth. There was no significant difference in third-degree perineal lacerations between midforceps and the matched low forceps group in this study.

The increase in cephalohematomas and depressed 1-minute Apgar scores in the midforceps delivery group compared to the entire population is of concern and indicates risk associated with the midforceps group. There was no significant difference in cephalohematomas, however, between the midforceps groups and the matched low forceps group. This discrepancy may be related to the different sample sizes in the two analyses. No significant differences were noted in other short-term measures of neonatal morbidity except for the 1-minute Apgar score, which was lower in the midforceps group. The matched groups therefore appear to represent groups at some risk for some abnormal short-term outcome, which appears to be unrelated to the method of delivery.

There was no evidence of greater neonatal morbidity in the midforceps groups when the immediate indications for the midforceps deliveries were divided into fetal distress and dystocia and compared to matched cesarean section patients. The only significant difference was a higher incidence of low 5-minute Apgar scores in the fetal distress group delivered by cesarean section. Other outcome measures, while not significantly more frequent in the midforceps groups, may be significant in a larger series.

The association of epidural anesthesia with midforceps delivery has been noted previously and is again confirmed here. Epidural analgesia may be associated with a temporary slowing of labor during either active or second stage and with delay in descent and rotation.[5] Heart rate decelerations may also follow the administration of an epidural dose.[6] These changes tend to be transient and are not usually associated with the development of fetal acidosis. Eliminating epidural anesthesia may result in fewer midforceps deliveries, but this was not a randomized study and selection bias may have been present. Conclusions regarding epidural anesthesia would therefore be speculative. When the midforceps delivery group was matched for weight, gestational age, dystocia, and heart rate abnormalities and compared to low forceps delivery and cesarean section

Table IX. Comparison of midforceps delivery group with other matched groups

	Midforceps delivery (%)	*Low forceps delivery (%)*	*Cesarean section (%)*	*Spontaneous birth (%)*
Third degree perineal laceration	45	45	–	7*
1-min Apgar score <7	32	23†	34	15*
Shoulder dystocia	2	1	–	3
Cephalohematoma	7	3	2†	2†
Seventh nerve palsy	1	2	–	–
Seizures	1	1	1	1

*$p < 0.00001$.
†$p < 0.05$.

cases, most differences were not significant, indicating some risk associated with the condition leading to midforceps delivery rather than solely being related to the delivery technique.

This study does not imply that midforceps delivery is free of risk but merely that in our experience the judicious use of midforceps has not been associated with increased short-term risk. Liberalization of the indications for midforceps delivery may be associated with increased morbidity. We do not advocate liberal use of midforceps, which has been shown by others[2] to be associated with increased risk of fetal injury.

The most important question regarding long-term infant outcome remains unanswered by this study. A long-term follow-up study of these matched groups is in preparation.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. B. D. REEVES, El Paso, Texas. My reasons for wanting to discuss this paper were twofold. First, its subject is a timely one. Second, the staff of its site of origin and Dr. Rosen in particular have made considerable previous contributions to our specialty.

In a recent publication Howard C. Taylor, Jr., reviewed "Changes in Academic Obstetrics in the Last Twenty-five years."[1] The review was formally discussed by Louis M. Hellman. Both of these men have made even more considerable contributions. Dr. Hellman comments, ". . . let me violate the historical boundary set us and glance at the past as the base for what has been a fundamental change from an exquisite and often dangerous mechanical art to a greatly simplified approach to childbirth, namely: if you see or suspect trouble coming, deliver by cesarean section . . . . Gone are the complicated forceps delivery, the difficult breech extractions, the two-, four-, and five-day labors . . . . "[1]

The questions in the minds of these authors particularly relating to midforceps deliveries are Are they gone?, To what extent?, and Why? The authors assert in their introduction that midforceps are "still relatively common," but state in their hypothesis, however, that the "conservative" use of them "was not associated with increased neonatal morbidity and was associated with acceptable maternal morbidity." They go on to say, "liberal use of midforceps . . . has been shown by others to be associated with increased risk of fetal injury".

My interpretation of this paper is that the authors' analyses of their data, their references' data, and the logical, rhetorical, and statistical support for their hypothesis have not been accomplished to the degree that they—and I—would like to see. The reasons for this reservation are outlined extensively in a recent article by Bailar et al.[2]

Time does not permit a review of that article—which I recommend to all of you, since it applies so well to clinical obstetric research, which rarely permits pure internal, randomized, and parallel or cross-over control studies. My central concern in this paper is the control group.

The question is not whether "conservative" or "liberal" use of midforceps carries with it a more ominous prognostication for fetal outcome. Rather, the question is whether midforceps however used are inherently more dangerous than the alternate means of delivery, which is cesarean section. In this study cesarean section becomes the primary external control factor for assessing fetal outcome of midforceps delivery. Therefore, incidentally, comparing maternal morbidity as was done here becomes moot. Their other results could be made more clear if compared with cesarean section deliveries, which then would make their χ^2 analyses and probability factors more meaningful.

For example, their Table VI, which assesses indications for midforceps deliveries compared to cesarean sections and for dystocia or fetal distress, would be more meaningful if it were posed as a comparison to "all patients." Normal spontaneous vaginal deliveries and, for the most part, low forceps deliveries are not comparable to midforceps in either indication or outcome. Also, comparing "elective" use of midforceps in this vein means nothing. Tables I, III, and V (labor abnormalities, intrapartum-associated risk factors, and neonatal morbidity) would take on far more meaning and therefore guidance in our decision analysis if analyzed in comparison to cesarean sections done for dystocia or fetal distress. Tables I and III deal with factors that are a priori to the deliveries by midforceps or cesarean section and in themselves may significantly relate to fetal outcome. Table V, concerning neonatal morbidity, can only take on significant meaning if compared with cesarean section as the alternate delivery method. Table IX, because of its comparison with cesarean section deliveries, is the most useful and supportive of their hypothesis, but in light of incompletely related external controls a good part of it contains comparisons that are less useful.

I would urge the authors to review their data and analyses. I would encourage them to look at the article by Bailar et al., not only for its value in reviewing this paper, but also for its potential for a prospective study—one that might aid in placing midforceps delivery in current perspective as to its optimal use, its risks and benefits, and, particularly, the circumstances in which it is indicated.

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Dr. Douglas W. Laube, Iowa City, Iowa. One hundred seventy-six midforceps operations occurred at a time when there was a marked increase in the national trend toward cesarean section, a trend also observed in this study population.

There are published reports claiming that midforceps delivery is associated with a poorer maternal and infant outcome.[1, 2] Others suggest that the maternal and infant outcome for babies delivered by cesarean section, the logical alternative to midforceps delivery, is worse than that for the midforceps delivery.[3]

All studies have limiting factors in common including lack of prospective long-term follow-up of the children and lack of control for confounding variables such as labor abnormalities, intrapartum fetal acidosis, and conduction anesthetic use. The literature also contains conflicting interpretation of data from collaborative studies derived from the care of patients a generation ago.[4, 5] It may well be that the dangers reportedly attributed to the procedure of midforceps delivery may in fact be the result of the conditions requiring its legitimate cause.

I have a specific question regarding the frequency of midforceps use and the level of training of the operator. The incidence of this operation was 0.8% in the period studied, with 74% (Table VII) of these procedures done by residents and 26% by more senior operators. Did the authors analyze infant and maternal outcomes when subdividing their results into groups based on level of training?

The authors are consistent with others in presenting data describing confounding variables associated with midforceps operation, in particular, the labor abnormalities preceding the operation itself (Table I). Most active-phase and second-stage dystocias were reported as significantly more frequent in the midforceps delivery group. In view of the high association of midforceps delivery and dystocia to a similar subset of patients delivered spontaneously or by cesarean section with similar percentages of dystocia? A more strict comparison of this nature might help to answer whether it is the operation itself or the conditions leading to the operation which are the problem. Intrapartum fetal asphyxia similarly could be analyzed and compared with neonatal outcome. Did the authors perform studies of umbilical cord blood gases and pH in an effort to assess the true metabolic condition of the newborn infant?

The study describes a relatively small number of immediate neonatal complications with potentially serious sequelae including seizures, shoulder dystocia, brachial palsy injury, and seventh nerve palsy and showed no significant difference in these outcomes. The only significant difference in the study group of newborn infants involved problems that are less serious such as the low 1-minute Apgar score and cephalohematoma. It is interesting to note (Table VI) that there is no difference in the incidence of cephalohematoma in infants of the control group when dystocia was taken into consideration.

The investigators found that the use of epidural anesthesia was significantly different in the patients studied (51% in the midforceps group and 20% in the control group). This issue needs further attention in future research efforts of this subject. It is possible that this labor anesthetic is directly associated with, if not responsible for, a significant part of the rise in cesarean section and forceps delivery. It is unlikely that the practicing obstetric community can expect a low cesarean section rate, a low forceps rate, and a high epidural rate. Either we adopt a philosophy similar to that of our British co-workers where epidural rates are in the 2% to 3% range and the primary cesarean section rate is in the 5% to 6% range, or we accept a 40% epidural rate and a 30% cesarean section rate. A reasonable middle ground might be achieved if obstetricians are trained to become expert in the indications and use of midforceps. Did the authors separate the epidural patients into those who had epidural anesthesia instituted during uncomplicated labor from those who had it placed with dystocia in preparation for oxytocin?

My last question is perhaps speculative in nature. Do the authors have any data regarding the number of malpractice allegations brought against the obstetricians of the midforceps group? This is asked because of the prevailing unfavorable medical legal undertow that often clouds medical judgement. As is well known, malpractice precedent has been set for liability imposed on a physician for injury to the mother or infant resulting from the unnecessary or negligent use of forceps during delivery.[6]

In closing, I am appreciative of the opportunity to discuss the findings of this study. I think that it is important to continue research on this topic, and I do not yet believe that carefully selected midforceps operations should be relegated to the pages of obstetric history.

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DR. ROBERT J. SOKOL, Detroit, Michigan. I would like to respectfully disagree strongly with what the first discussant, Dr. Reeves, said about the study design.

Although I have not had an opportunity to see this manuscript, it is clear that this study uses very standard epidemiologic study techniques. Doing a prospective randomized clinical trial on midforceps deliveries would probably be absolutely impossible in the 1980s. It was probably impossible at any time. That does not mean that, with appropriate epidemiologic study techniques and statistical management of the data, you cannot draw reasonable conclusions.

The first part of the study appears to me to have been performed by means of what is called an historical prospective cohort study technique. With use of this design, a group of "at-risk" patients is compared with everybody else in a sample. This allows a direct calculation of relative risk, a considerable advantage.[1] Although a cohort design is not very efficient statistically, it has the additional advantage that it really shows very clearly how patients with a particular risk, in this case midforceps delivery, compare with everybody else.

A matched design, also used in the current study, is statistically more efficient than the cohort approach[2] and can provide a somewhat more detailed, precise look at the data by controlling for confounding by the matching factor(s). Both of these study designs are widely used and well accepted. Certainly, it is unfair to suggest that the design of the current study is inadequate and that you cannot infer anything from it.

In studying something as rare as midforceps deliveries, some clinically important differences between groups could be missed because of limited sample size. In this study the 176 midforceps deliveries constitute a relatively large sample, providing reasonable power. Clinically important effects of midforceps delivery would probably not be missed, although adverse consequences of midforceps delivery for individual infants are not ruled out.

I believe that this is a very important study. Clearly, midforceps should not be used frequently or excessively, but even in 1984 their use is certainly not absolutely contraindicated. It seems to me that this is a very important inference from the standpoint of medicolegal considerations.

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DR. HERMAN D. WEBSTER, JR., New Orleans, Louisiana. I have not been involved in a resident training program for the last 5 to 6 years. My concern is that of residents coming out of training programs now who have never seen a forceps rotation, much less done one. They are taught to deliver the patient of her infant posteriorly or to do a cesarean section. There is a difference in a difficult midforceps and an easy midforceps delivery, and I think there is still a place for it and that it should not be eliminated completely as is being done now.

DR. KENNETH L. NOLLER, Rochester, Minnesota. I have one question about the study design.

In my mind the matched part of the study is the more important, and I noticed that you matched according to labor pattern. This completely eliminates any chance of your doing a multivariate analysis to determine whether or not these problems were associated with the labor or with the midforceps delivery.

I am curious why you chose that approach.

DR. SAM P. PATTERSON, Memphis, Tennessee. Dr. Laube's suggestion that all residents be well trained in midforceps delivery is unrealistic in 1984. If we have, as he has suggested, a <1% incidence of midforceps delivery with the large training programs such as the one in Memphis with 36 residents and 5000 or 6000 deliveries, then there are four or five per resident in his training program. So I do not think we can really make our residents proficient in midforceps delivery.

My big problem, as it is for you who are still delivering babies, is having a deep transverse arrest with an epidural anesthetic in a nulliparous patient who has been in the second stage for 2 or 3 hours. I wonder if this is really the best course for these patients? With deep transverse arrest, the medicolegal atmosphere that we are in, deep transverse arrest, even though we are proficient at delivery of these patients, must be relegated to the past. Midforceps delivery is not in the best interest of us or these patients. Deep transverse arrest is now best managed by abdominal delivery.

Dr. Dierker (Closing). I would like to thank Dr. Reeves for his comments. I would like to thank Dr. Sokol even more for his. I am glad he came this morning. I do want to thank Dr. Reeves for sending me a copy of the article which he quoted today.

Regarding the need for internal controls, I agree completely, and I think that the best and most scientific way to really look at the outcome measures for midforceps delivery is to do a prospective randomized study. I also agree that this is probably not possible in my lifetime because randomizing treatment to patients who present in labor with a breech presentation is a lot different than trying to randomize treatment to patients in the second stage who have been pushing for a couple of hours or when there is a fetal heart rate of 60.

I think a lot of emotion goes into the decision sequence, and I think doing a randomized prospective study under those circumstances is probably not possible.

Regarding the need for internal controls, I reviewed the paper that Dr. Reeves quoted. It is a good paper and should be reviewed by all of us. It lists five questions whose answers provide preliminary indication of the strength of the evidence provided by an externally controlled clinical study.

These five questions, for which we felt that we scored relatively well, are as follows: (1) Does it appear that the intervention was applied with the primary intent of affecting the outcomes reported such as cure, survival, or the incidence of complications? (2) Is it clear that the authors' intent to analyze and report their findings preceded the generation of the data, though the data may have been gathered for a different primary purpose? (3) Have the authors shown that they had a plausible rationale for their interpretation of the data before the data were inspected or the analyses undertaken? (4) Would the results have been interesting, and publishable, if they had been different from those obtained? In other words, would negative findings have a chance of being reported? (5) Do the authors present reasonable grounds for analyzing their results?

We scored our results on a basis of 1 to 5 and felt that we had scored about 3.5. That was a subjective rating, however.

Regarding Dr. Laube's comments, we did analyze infant outcomes with the level of training of the clinician, primarily the cephalohematoma and the low 1-minute Apgar score. These were increased in the first year resident level and were decreased at the faculty level.

The second question, did we compare the group with midforceps delivery for dystocia to a similar subset delivered by cesarean section? We matched groups for dystocia, heart rate abnormality, weight, and gestational age and will compare long-term morbidity in a subsequent study.

Did we compare umbilical blood gases and pH with a scalp pH? No, we did not. We are doing this.

Was there any overlap in the small number of babies who had abnormalities such as shoulder dystocia, brachial palsy, and seizures? In other words, did a few babies have multiple abnormalities?

There was no overlap in the midforceps group with the number of specific outcome abnormalities. There was overlap between shoulder dystocia and brachial palsy in one of the low forceps patients.

Concerning epidural anesthesia, did I determine whether it was given before or after a labor abnormality? No, I did not. Epidural anesthesia was given during the active phase of labor and rarely initiated late in the second stage of labor.

Regarding the last question, there are no malpractice allegations against the midforceps deliveries.

Regarding Dr. Noller's question about the matched group, we chose the matched comparison of midforceps deliveries, matching for labor abnormality, heart rate abnormality, weight, gestational age, sex, and race so that we would eliminate as many of the confounding variables as possible. We did this after consultation with the statistician who felt that this would be the strongest way to look at the data we have. Regarding Dr. Patterson's comments about residency training, I agree. We have not gotten the final answer on long-term neurological outcome. If we find that midforceps seems to be a reasonable tool in our armamentarium, we still do not plan on increasing our midforceps use. We do not plan to perform midforceps deliveries merely for residency training. Residents are welcome to scrub with us and we scrub with them on difficult procedures whether it is for cesarean section, hysterectomy, or midforceps delivery. We do not do procedures strictly for resident training but for clinical indications in the best interest of the patient.

I would like to thank the reviewers for their comments and the audience for their interest.

Eclampsia

IV. Neurological findings and future outcome

Baha M. Sibai, M.D., Joseph A. Spinnato, M.D., Dottie L. Watson, M.D., James A. Lewis, M.D., and Garland D. Anderson, M.D.
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Sixty-five patients with eclampsia were longitudinally evaluated regarding neurological abnormalities and maternal outcome (6 to 42 months) after eclampsia. Electroencephalograms were obtained on all patients during the subsequent 6 months. Computerized axial tomographic scans (n = 20) and cerebral arteriograms (n = 3) were obtained on patients with neurological deficits and/or those with an atypical clinical course. The electroencephalogram was abnormal in 49 patients (75%) at initial assessment but gradually returned to normal in all observed patients within 6 months. Cerebral arteriograms and computerized axial tomographic scans were normal in each patient studied. None of the patients had neurological deficits or subsequent convulsions on follow-up examination. Thirty-eight patients had one or more subsequent pregnancies without recurrent eclampsia, but 14 (37%) had pregnancy-induced hypertension. The findings suggest that neurological events of eclampsia are acute and transient and that long-term neurological deficit is rare in the properly managed patient. Computerized axial tomography and electroencephalography are rarely indicated in the management of such patients. (AM J OBSTET GYNECOL 1985;152:184-92.)

Key words: Eclampsia, EEG, CAT scan, neurological findings

Eclampsia is defined as the occurrence of convulsions and/or coma in patients with signs and symptoms of preeclampsia. The cause of the convulsions or coma is unknown. Some of the factors suggested in the etiology are cerebral vasospasm or hemorrhage, cerebral ischemia, cerebral edema, or hypertensive encephalopathy.[1] In addition, cerebral abnormality in the form of edema and/or hemorrhage is a common autopsy finding in patients with eclampsia.[2] Despite the importance of cerebral findings in eclampsia, the modern obstetric literature is virtually void of any information regarding the electroencephalographic (EEG) or computerized axial tomographic (CAT) study of such patients. As a result, the available information is "dated" by its outmoded equipment and less sophisticated technique and interpretation.

There are sporadic case reports[3-5] describing CAT scan findings in patients with eclampsia. In addition, there are a few reports[6-10] describing EEG findings in the prodrome or acute phase of eclampsia. Of the information available, there are minimal prospective data describing the neurological findings in patients with eclampsia and the remote fate of abnormal EEG findings in such patients.[11, 12] A report by Sexton[13] suggested a correlation between eclampsia and future development of epilepsy.

The aim of this prospective investigation is severalfold: (1) to report the short-term neurological and EEG findings in patients with eclampsia, (2) to correlate these EEG findings with maternal mean arterial blood pressure, (3) to report the remote fate of abnormal EEG findings in such patients, (4) to report the CAT scan findings in a select group of patients with complicated eclampsia, and (5) to report the follow-up neurological outcome in patients with eclampsia.

Material and methods

Sixty-five patients with eclampsia were studied regarding neurological and EEG findings (n = 65), CAT scan findings (n = 20), and neurological outcome after eclampsia. The management of these patients was not altered by the study. Initial EEG recordings were obtained during the first 48 hours of hospitalization and were then obtained serially during the subsequent 6 months. The initial electroencephalogram was recorded ante partum in 30 patients and post partum in the remaining patients. At the time of the initial EEG recording, the patients were receiving intravenous magnesium sulfate according to a protocol that included a loading dose of 4 gm of magnesium sulfate

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gm in 250 ml of 5% dextrose in lactated Ringer's solution infused intravenously, followed by a maintenance dose of 2 to 3 gm/hr. Some patients were also receiving continuous intravenous hydralazine to maintain the diastolic blood pressure between 90 and 110 mm Hg. The EEG technique included the use of a 21-lead monopolar recording with the ipsilateral ear or the average reference as a reference point. The potentials were recorded with either a 16- or 20-channel EEG recorder. The records were then analyzed for frequency, amplitude, waveform, and presence of spike activity. In patients with abnormal EEG findings, the electroencephalogram was recorded again in 1 week (n = 46) and, if persistent, in 6 weeks (n = 30) and again in 3 to 6 months (n = 6).

Patients with an abnormal neurological examination and/or focal or lateralizing findings on electroencephalogram and patients in whom the clinical course was considered atypical were evaluated with CAT scans (n = 20) and/or cerebral arteriography (n = 3). The CAT scan was obtained with and without contrast material to rule out cerebral hemorrhage and/or cerebral edema. Cerebral arteriography was obtained to rule out cerebral venous thrombosis or cerebral vascular malformations. The mean arterial blood pressure was calculated for each patient at the time of EEG recording and results were then correlated with EEG findings.

Eclampsia was considered atypical or complicated if the patient continued to have convulsions while receiving adequate doses of magnesium sulfate, if the onset was late post partum, or if there was associated neurological deficit. Such patients had extensive neurological evaluation to rule out other causes of convulsions.

Maternal outcome and follow-up. Early follow-up (first 6 weeks) was done at our obstetric clinics, while later follow-up data were obtained from our clinics, local physicians, and local health departments. All patients with an initially abnormal EEG and/or abnormal neurological finding had their follow-up evaluation at our clinics. Maternal evaluation included an interval history with special emphasis on history of convulsions and/or neurological deficit, use of anticonvulsive and/or antihypertensive medications, and future pregnancy outcome. In addition, all data pertaining to blood pressure measurements during subsequent physical examinations and/or pregnancy were obtained.

Results

The mean age ± 1 SD of patients studied was 18.2 ± 4.0 years (range 13 to 32 years), and 56 patients (86%) were less than 25 years of age. Fifty-six patients (86%) were nulliparous and nine (14%) were para 1 or more. Fifty patients (77%) were black, 14 (21.5%) were white, and one was Haitian. Eclampsia developed before delivery in 51 patients (78.5%) and postpartum in 14 patients (21.5%). Six patients had previous history of chronic hypertension and/or renal disease (two of whom had sickle cell disease), one patient had Class A diabetes, and one patient had tricuspid atresia. This last patient had undergone surgical correction of the cardiac malformation during childhood.

Table I. Neurological findings in patients with eclampsia (n = 65)

Neurological finding	*No.*	*%*
Transient neurological deficit	3	5
Transient cortical blindness	3	5
Normal CAT scan findings	20/20	100
Normal cerebral arteriograms	3/3	100
Deep comatose state*	1	1.5
Abnormal EEG findings	49	75

*Maternal death at 8 weeks post partum.

Table II. Type of abnormal EEG activity in patients with eclampsia (n = 49)

EEG activity	*No.*	*%*
Excessive diffuse slow activity	33	67
Focal slow activity	16	33
Paroxysmal spike activity*	5	10
Flat (silent) recording†	1	

*Intermixed with either diffuse or focal activity.
†Maternal death at 8 weeks post partum.

Table I summarizes the initial neurological findings in all patients studied. There was no evidence of either cerebral edema or cerebral hemorrhage in any of the CAT scans obtained in the 20 patients with complicated or atypical eclampsia (three patients had transient neurological deficit, three patients had transient cortical blindness, and one patient was neurologically unresponsive). Cerebral arteriograms were normal in all three patients with transient neurological deficit. None of the patients had neurological deficits at time of discharge from the hospital. The one patient in deep coma eventually died at 8 weeks post partum. Consent for autopsy examination was denied by the family.

Forty-nine patients (75%) with eclampsia had abnormal EEG findings. All these patients had adequate serum magnesium levels (4.5 to 11 mg/dl) at the time of EEG examination. Table II describes the type of EEG abnormality recorded in such patients. Observed abnormalities were both diffuse and focal. The one patient with a flat (silent) EEG recording was the patient in deep coma mentioned previously. At the time of initial EEG recordings the average mean arterial blood pressure in patients with abnormal EEG findings was 116 ± 8.4 mm Hg versus an average mean arterial blood pressure of 114 ± 9.3 mm Hg in the group with normal EEG findings. This difference is not statistically

Table III. Serial EEG findings

Time of EEG recording	*Normal*		*Abnormal*	
	No.	*%*	*No.*	*%*
Initial (n = 65)	16	25	49	75
1 wk (n = 46)	15	33	31	67
6 wk (n = 30)	23	77	7	23
3-6 mo (n = 6)	6	100	0	

significant. The average mean arterial blood pressure during the second trimester was calculated in 52 patients. There was no significant difference between patients with abnormal EEG findings and those with normal EEG findings regarding the percentage of rise in mean arterial blood pressure from the second trimester to the blood pressure level at time of EEG recording.

Maternal outcome and follow-up. Table III summarizes the serial EEG findings in all patients. It is interesting to note that EEG abnormalities persisted for as long as 6 weeks post partum in seven patients. These abnormalities returned to normal in all six patients studied at 3 to 6 months. The other patient died at 8 weeks post partum with a flat EEG recording. In patients with persistent EEG abnormalities, the return to a normal pattern was a gradual phenomenon. In addition, the abnormal EEG findings persisted in spite of the fact that maternal blood pressure had returned to the normotensive range.

One patient died at 8 weeks post partum after admission in a moribund state. This patient had antepartum eclampsia and sustained multiple convulsions during transfer to the perinatal center. After stabilization and control of convulsions with magnesium sulfate, she was delivered by cesarean section for fetal distress. Immediately after operation she was comatose and had disseminated intravascular coagulopathy. Her postpartum course was complicated by sepsis, continued seizures, and pulmonary insufficiency. On the second postoperative day an EEG recording demonstrated absent cortical activity. A CAT scan failed to demonstrate abnormal findings. Cerebral arteriograms were not obtained because of the patient's unstable condition. She never regained consciousness and died. Permission for autopsy examination was denied by the family.

One additional patient died at 9 weeks post partum after admission to a local hospital with bronchitis, congestive heart failure, and deep vein thrombosis. The patient died 1 week after hospitalization and autopsy findings revealed multiple pulmonary emboli. This patient had tricuspid atresia with secondary pulmonary hypertension. She developed intrapartum eclampsia while receiving intravenous magnesium sulfate. She had a spontaneous vaginal delivery at 34 weeks of gestation. The initial EEG recording was abnormal but returned to normal within 1 week, and she was normotensive at the time of discharge from our hospital 10 days post partum. Her post partum checkups 2 weeks after discharge and 6 weeks post partum were uneventful.

None of the remaining 63 patients required anticonvulsive medications at the time of discharge from the hospital; however, 11 patients required antihypertensive medications for control of hypertension. Four of the 11 patients were normotensive 2 weeks later; the remaining seven patients were still hypertensive at 6 weeks post partum. Six of these seven patients were receiving medications for chronic hypertension before pregnancy; the remaining patient was referred for evaluation of hypertension.

Fifty-one of 63 surviving patients had follow-up data available at 6 to 42 months after eclampsia. The other patients were lost to follow-up. None of the patients studied had any evidence of neurological deficit or subsequent convulsions during this time period. Seven patients (same patients mentioned previously) were still receiving antihypertensive medications for treatment of chronic hypertension. None of the remaining patients had evidence of hypertension after their pregnancies.

Thirty-eight patients had one or more subsequent pregnancies without recurrent eclampsia. Twenty-four of the 38 patients (63%) were normotensive during the first pregnancy after eclampsia, while the other 14 (37%) had pregnancy-induced hypertension (seven had mild hypertension and seven severe). Three of the seven patients who subsequently had severe preeclampsia had chronic hypertension. All three patients had either stillbirths or neonatal deaths during eclampsia as well as in the subsequent pregnancy. All three patients were more than 25 years old and all three underwent tubal ligation on request. Two additional patients with chronic hypertension underwent voluntary tubal ligation after eclampsia and poor perinatal outcome. The other patients with previous history of chronic hypertension had good perinatal outcome during eclampsia and are pregnant at the present time.

Comment

The electroencephalogram indirectly measures electrical activity of the brain, recording impulses received transcutaneously by electrodes applied on the scalp. Many cortical phenomena that do not simultaneously activate large areas of cortex fail to become evident at the scalp and hence will not be recorded on an electroencephalogram. During the past 20 years the English language obstetric literature is virtually void of any new information regarding the EEG findings in eclampsia. Rosenbaum and Maltby[6] reported that 13 of

20 patients with eclampsia and two of 20 patients with preeclampsia had abnormal EEG findings obtained 1 week to 5 years after the pregnancy episode. In addition, they found a sixfold increased likelihood of a family history of convulsive disorder in patients with eclampsia versus those with preeclampsia. They concluded that patients with eclampsia had a constitutional predisposition to convulsions and suggested that a family history of convulsions plus an abnormal EEG finding during pregnancy might detect patients who are at increased risk for the development of eclampsia. However, their patients were apparently selected from a psychiatry-neurology clinic, thus possibly skewing the incidence of persistent convulsive disorders in both groups. Serial EEG recordings were not obtained and the interval between eclampsia and the observed abnormal EEG recording may have been too short to rule out possible residual acute effects in several of their patients.

Parviainen et al.[7] reported on two patients with marked cerebral dysrhythmia that resolved after a few days' treatment with ammonium chloride. Jost[8] studied the EEG findings in nine patients with eclampsia during and several days after eclamptic seizures. He reported that EEG abnormalities are directly related to the severity of maternal hypertension. In addition, he found an improvement in the clinical picture and EEG findings when maternal blood pressure was lowered to the normotensive range. McIntosh[9] noted cerebral dysrhythmia in five of six patients with eclampsia when the EEG recording was obtained several days after the last seizure. Poidevin[10] noted dysrhythmia in 10 of 12 patients with eclampsia tested 10 to 14 days post partum. Kolstad[11] reported on two patients with eclampsia in whom the EEG disturbances persisted 3 and 8 weeks after convulsions. In addition, he found no correlation between EEG abnormalities and blood pressure findings in 17 patients with preeclampsia/eclampsia studied. A recent reference to serial EEG findings after eclampsia introduced unpublished data by Zuspan during the discussion of an article by Fish et al.[12] He reported the presence of both diffuse and localized abnormal cerebral activity that persisted for as long as 6 to 8 weeks before disappearing.

Seventy-five percent of patients with eclampsia in this study had abnormal EEG findings within 48 hours after convulsions. It is of interest to note that these abnormalities were demonstrated during the administration of therapeutic doses of magnesium sulfate.[14] The observed abnormalities were both local and diffuse slowing of various degrees of severity. The most consistent change was a diffuse slowing ranging from a slowing of the α-wave rhythm to generalized δ-wave slowing. Paroxysmal spike activity was observed infrequently. All of these abnormalities are nonspecific and have been reported in several other disorders including polycythemia, hypoxia, renal disease, hypocalcemia, hypercalcemia, and water intoxication. The gradual return to normal of EEG findings observed in this study is similar to that described by Zuspan (see reference 12). The persistence of an abnormal EEG recording 1 week after delivery in 31 of 46 patients studied is not surprising and might provide an explanation for the syndrome of late postpartum eclampsia.[15] This information prompts us to again suggest that eclamptic seizures can occur later in the postpartum period than is suggested in standard obstetric textbooks. It is important to note that these EEG abnormalities were recorded at a time when most of the above patients were normotensive. In addition, all seven patients with abnormal EEG recordings at 6-week follow-up had normal blood pressure readings at the time of EEG recordings. These findings do not suggest any correlation between EEG abnormalities and blood pressure. Such findings are similar to those reported by Kolstad[11] but are in disagreement with the conclusions of Jost.[8]

Some obstetric units recommend the use of short-term phenobarbital therapy when parenteral magnesium sulfate is discontinued in hospitalized patients with eclampsia during the immediate postpartum period. This recommendation would appear to be a reasonable practice in view of the persistent EEG abnormalities in 31 of the 46 patients studied. However, the efficacy of such therapy has not been studied in a controlled manner. On the other hand, some internists and neurologists prescribe long-term anticonvulsive therapy (as for epilepsy) for the majority of patients with eclampsia (especially those with postpartum eclampsia). The persistence of an abnormal EEG recording in only seven of the 65 patients at 6 weeks post partum and the eventual return to a normal recording in all patients studied lend little support for such practice.

CAT scanning is rarely used in the management of patients with eclampsia. Benedetti and Quilligan[3] reported on one patient with eclampsia with reduced lateral ventricular size when a CAT scan was obtained. Cerebral edema was diagnosed and the patient improved after treatment with fluid restriction and dexamethasone. Beeson and Duda[4] reported CAT scan evidence of diminished density of occipital lobe white matter presumed to represent cerebral edema in a patient with eclampsia with sudden loss of vision. The patient was treated with mannitol and dexamethasone. Repeat CAT scan demonstrated reversal of the previous findings. On the basis of that report they suggested obtaining CAT scans in the immediate postpartum period as part of the management of patients with eclampsia. Similar recommendations were suggested by Donaldson.[1] Beck and Menezes[5] reported on a patient with eclampsia with bilateral periventricular subependymal hemorrhage when a CAT scan was performed. The patient was treated with magnesium sulfate, dexamethasone, and fluid restriction. Bilateral carotid and vertebral angiography showed diffuse spasm of the intracranial vessels. Repeat CAT scan 2 weeks later showed a dense subependymal hematoma. They suggested that a CAT scan be performed only in patients with eclampsia with focal neurological signs.

Neither cerebral edema nor cerebral hemorrhage was observed in any of the 20 patients with eclampsia studied by a CAT scan in this series in spite of its selective use in the more seriously ill patients and/or those with atypical symptoms. In fact, three of these patients had transient cortical blindness with clinical findings similar to that of the patient described by Beeson and Duda.[4] Three additional patients had focal neurological findings similar to those of the patient described by Beck and Menezes.[5] The absence of demonstrable cerebral edema or hemorrhage by CAT scan in this study represent the true absence of such findings in patients with eclampsia or it may be the result of the limitations of CAT scanning in detecting minimal cerebral abnormalities. It is our opinion that the normal findings in these patients neither challenge nor disprove the possible role of cerebral edema and/or minimal hemorrhage in the production of eclamptic seizures.

The long-term follow-up of patients after eclampsia was the subject of a unique and remarkable study by Chesley et al.[16] This study included follow-up of 267 women for 40 years after eclampsia. The authors found remote mortality rates to be increased among multiparous women who had eclampsia but not increased among these who had eclampsia in the first pregnancy. Similar differences regarding the incidence of future chronic hypertension were found between women who had eclampsia in first pregnancy and those who were multiparous when they had eclampsia. The authors concluded that eclampsia does not cause chronic hypertension in the future. In 1976 Sexton[13] reported on eight patients who developed epilepsy several years after complicated childbirth. Six of the eight patients had eclampsia and the other two had complications of hemorrhage, shock, and sepsis. Consequently the author suggested that eclampsia is a significant cause of epilepsy in the future. However, the above patients were apparently selected from a group of mismanaged and neglected cases of eclampsia.

The findings of this study regarding future development of chronic hypertension and subsequent pregnancy outcome are similar to those reported by Chesley et al.[16] The neurological findings on follow-up for 6 to 42 months do not suggest any relationship between eclampsia and future development of epilepsy. These findings are in disagreement with the conclusions of Sexton,[13] which might reflect the difference in management of patients with eclampsia.

In summary, eclamptic seizures are the result of an acute event that has little relation to prior or subsequent neurological events. The EEG recording is acutely abnormal in the majority of such patients. There is no relationship between the extent of EEG abnormality and degree of maternal hypertension. The resolution of these EEG changes occurs gradually and is complete in virtually all patients. It would seem unnecessary to perform EEG recording in patients with eclampsia except in rare instances. Eclampsia is rarely associated with any demonstrable abnormality by CAT scan, and its use should be restricted for evaluation of patients with late-onset postpartum eclampsia and/or those patients with associated neurological deficit. There are no long-term neurological deficits in the properly managed patient with eclampsia.

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Discussion

Dr. James N. Martin, Jr., Jackson, Mississippi. Things in obstetrics tend to run in cycles. Trends in research activities tend to parallel the availability of new or better tools with which one can investigate old dilemmas. An earlier cycle of great activity surrounding EEG changes related to eclampsia dates from the 1950s and early 1960s. In the 1980s the cycle has returned with a resurgence of interest in the study of patients with eclampsia and the use of upgraded EEG equipment as well as CAT scanning.

Dr. Sibai's presentation today is another contribution from the excellent obstetric unit in Memphis from which have come several recent investigations pertinent to the study of eclampsia. In the project reported today the investigators prospectively studied 65 patients with eclampsia using serial EEG recordings as well as selected CAT scan and cerebral arteriographic studies. All study subjects received concurrent magnesium sulfate and all EEG studies occurred after the eclamptic episode. As noted in earlier investigations by Dr. Sibai, EEG findings were not influenced by magnesium sulfate infusion.[1] Follow-up EEG studies were performed as long as 6 months later on virtually all study subjects. Let us consider first the EEG information and second the CAT scan data.

Since the electroencephalogram is a several million times magnified record of the resting electrical state of the brain's cortical cells, one wonders not why 75% of patients with eclampsia in this study had abnormal EEG recordings but rather why 25% did not demonstrate abnormal α-wave rhythms, frequencies, and/or voltages. Did EEG abnormalities correlate with other parameters such as preterm versus term gestation or antepartum versus early or late postpartum eclampsia? Although EEG abnormalities in this investigation were not found to be directly related to the severity of maternal hypertension, were they correlated with the mean change in blood pressure elevation above individual baseline values? Do the investigators consider generally abnormal EEG findings to be a factor in the choice of antihypertensive agents for these patients, especially for extended therapy? Finally, what is the current practice at Memphis regarding use of oral anticonvulsants for these patients when magnesium sulfate infusion is discontinued?

Recall that 20 of the 65 patients with eclampsia were evaluated further by CAT scanning if they had late postpartum eclampsia, an atypical clinical course such as convulsions persisting despite adequate magnesium sulfate, focal lateralizing findings on EEG recording, and/or abnormal neurological deficits such as transient cortical blindness. However, none of the 20 scans were considered abnormal. The apparent absence of abnormal findings on CAT scanning in this study raises some questions and deserves comment. Perhaps this outcome is a tribute to the excellent care afforded these patients, especially in regard to fluid management as well as avoidance of cerebral edema as described by Benedetti and Quilligan.[2] In contrast to the Memphis findings is a recent report describing two patients with eclampsia, who did not suffer severe visual symptoms but whose CAT scans were interpreted to be abnormal and to reflect cerebral edema.[3] Moreover, in eight related case reports of eclampsia complicated by significant visual compromise that have appeared during the last 6 years, five of nine CAT scan examinations were considered abnormal.[4-11]

This apparent disparity of findings prompts several questions related to CAT scans. What is the proper use of CAT scanning in the modern management of patients with eclampsia in these days of cost containment mixed with medicolegal entanglements? Dr. Sibai and his group indicate that it should be used infrequently, yet others such as Donaldson[12] advocate routine CAT scanning after all eclamptic episodes. Is the absence of abnormal findings secondary to the true absence of edema and/or perivascular microhemorrhage or is it secondary to the limited ability of CAT scanning to detect minimal cerebral abnormalities? Is it due to variations in radiologic interpretation? If cerebral edema were identified, do Dr. Sibai and his group feel that this information should alter patient care and require additional therapy? Finally, is there enough of a likelihood of another cause for an apparent late postpartum eclamptic seizure to warrant routine CAT scanning for assistance in differential diagnosis?

In their sixth periodic report, Chesley et al.[13] concluded that "eclampsia neither is a sign of latent hypertension nor causes hypertension." The authors' limited investigations presented today would also suggest that neurological alterations as evidenced by abnormal EEG findings do not persist long beyond the acute eclamptic episode and that eclampsia is not a progenitor of epilepsy. Perhaps, before this cycle of intense activity to study the neurological concomitants of severe preeclampsia/eclampsia is over, we can clarify further the appropriate clinical utility of these modalities for optimal patient care. The authors have made a beneficial contribution to our obstetric knowledge.

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DR. MORTIMER G. ROSEN, Cleveland, Ohio. This study on eclampsia, its neurological findings, and future outcomes is the fourth in a continuing series of reports by the authors relating to eclampsia. The authors have the remarkable opportunity to survey a large number of patients with eclampsia. Unfortunately, this also may speak to the lack of quality in medical care in some of the regions that funnel their patients into the hospital. Thus there is room for improvement. I note with interest that approximately one quarter of the eclamptic convulsions occurred in the postpartum period, perhaps suggesting that such improvement in prenatal care is taking place since there appears to be a higher percentage of postpartum convulsions as prenatal care improves.

The authors' purpose in the presentation is to describe the importance and appropriateness for the use of computerized tomography, electroencephalography, and arteriography in patients with eclampsia and, most important, to document the late neurological outcomes and future pregnancy performances in these patients.

I note that electroencephalography is used as the screening mechanism before the more morbid or more expensive procedures such as cerebral arteriography and computerized tomography are used. Because electroencephalography is the screening mechanism, we do not know if, in other patients, computerized tomography, for example, might show other lesions not found in this study. However, as I will note later, the screening process appears to be appropriate.

As the authors note, the electroencephalogram is really a summation of the electrical potential seen in individual cells. Unless focal lesions such as spike or sharp waves or marked asymmetries in voltages and wave frequencies are seen in the electroencephalogram, it cannot tell you the kind of problem that is present, the kind of drug that is present or the reason for the abnormality. The high incidence of abnormal findings in patients with eclampsia is not helpful in the management of most patients. As demonstrated in the authors' Table II, only one patient had an asymmetry such as a spike wave, and that patient later died. In the other patients with the more general electrical changes, do the authors feel the presence of magnesium sulfate, hydralazine, other barbiturates and analgesics, or other central nervous system–acting drugs that may have been used, may also have been responsible for the alterations in the electroencephalogram? A similar question may be asked of the seven patients who had abnormalities in the electroencephalogram at the 6-week postpartum follow-up examinations. Were these patients still medicated with central nervous system–acting drugs?

It was somewhat of a surprise to note that computerized tomography did not show any evidence of cerebral edema or hemorrhage. Is cerebral edema just a terminal finding, is it an important part of the precipitating events in the eclamptic convulsion, or is it not present at all? I note that it is common teaching that cerebral edema is present in eclampsia. Most recently, in an article by Kirby and Jaindl,[1] computerized tomography in two patients with eclampsia revealed increased intracranial pressure (obliteration of sylvian and basilar cisterns, slitlike third ventricle) and "scattered low densities" in the white matter in several areas of the brain. In addition, as quoted in *Obstetrical and Gynecological Survey*,[3] what happened to the abnormalities observed in patients who had died, which included ischemia secondary to platelet thrombi and arteriolar vasospasm? In addition, hemorrhaging, perhaps secondary to high blood pressure and small blood vessel obstruction, was seen.

I find it hard to understand that no neurological deficits were present at the time of discharge. I think the authors are referring to abnormal neurological findings on physical examination rather than to neurological deficits. It has been my experience that most patients do not remember the convulsive episode or the postconvulsive period. Indeed, with heavy medication these blank spaces in their memories may last for hours to several days in the postconvulsive period. Thus, although a small point, abnormalities in memory may still be present. One of my patients returned to my office 1 year later to request a visit to the hospital since her memory of the preconvulsive and postconvulsive time periods was blank.

In an earlier article, Sibai et al.[3] reported the effect of magnesium on the electroencephalogram as slowing of the α-wave rhythms to more prominent δ-wave rhythms.[1] In contrast, spike activity is more likely due to areas of injury. As noted earlier, I believe drugs may be one of the reasons for diffuse but nonspecific EEG findings. In addition, if the electroencephalogram is obtained in the postictal period, obviously it is going to be abnormal, once again possibly accounting for the large incidence of abnormal tracings.

The conclusions in this descriptive presentation are important. For example, the use of more sophisticated and expensive diagnostic techniques should not be considered unless the patient fails to respond to the usual care for patients with eclampsia or perhaps if the patient has specific focal neurological abnormalities.

Most importantly the authors document that despite the higher incidence of recurrent hypertensive disease of pregnancy in patients who have a history of eclampsia, the data allow for guarded optimism with respect to future pregnancy outcomes since the majority of the patients will be normal in the next pregnancy.

Finally and most encouraging is the finding that there were no long-term neurological abnormalities in the patients with eclampsia who did recover.

This study allows us to give better counseling information to patients with previous eclampsia and thus becomes important in clinical obstetric care.

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Dr. M. Gary Robertson, Grand Haven, Michigan. Could we get some information on the patient who died, particularly if a postmortem examination was done and how it correlated?

Dr. Sabai (Closing). In regard to Dr. Martin's questions, were there any differences between the patients who had early onset of eclampsia and those who had it after 36 weeks? We did not find any difference in the EEG findings between the two groups. Actually, the patient who ultimately died developed eclampsia at 39 weeeks of gestation.

In regard to the second question, were there any differences between the patients who had antepartum, early postpartum, or late postpartum eclampsia? Again, we could not find any difference in their EEG findings. I think this might be because the EEG findings are nonspecific. They are probably a reflection of some other type of physiologic changes that we still do not understand.

In regard to the question about the mean change in blood pressure from the values in nonpregnant women, we looked mainly at the mean arterial blood pressure during the second trimester, during the last visit, and at the time of electroencephalography. We correlated the mean arterial pressure during the last visit and at the time we did the electroencephalography. We did not find any difference between the groups who had abnormal EEG findings versus those who had normal EEG findings.

In regard to the question on oral anticonvulsive medications, after we discontinued magnesium sulfate we did not treat our patients with oral medication. I know there are some institutions that recommend the use of phenobarbital. I am not aware of any prospective studies that have shown that there is any benefit, so I do not know whether it works. Does it prevent convulsions in those who have late postpartum eclampsia? I cannot comment on that.

In regard to the value of the computerized tomographic scan in eclampsia, there were several case reports mentioned by Dr. Martin describing abnormal computerized tomographic scan findings, in the form of either edema and/or hemorrhage.

Our findings were surprisingly different from those of other published reports even though the computerized tomographic scan was done in patients who had atypical cases of eclampsia. We thought if there were any abnormal computerized tomographic scan findings we should expect to find them in patients who were very sick, those who had eclampsia late in the postpartum period, or those who continued to have seizures even though we were treating them with magnesium sulfate. We did not find any abnormal values. This finding is similar to the experience of Dr. Pritchard in Dallas. As commented by Dr. Martin, this difference might be related to the type of management these patients had had and the time we saw them.

Some authors suggested using mannitol when cerebral edema is demonstrated during computerized tomographic scan evaluation. I cannot comment on this, but I think it might be dangerous because there are two types of cerebral edema: the vasogenic and the cytotoxic. Mannitol might be helpful in one situation but dangerous in the second. We all know that there are some physiologic changes in patients with preeclampsia. For example, if the patient does not have good renal output, we might ultimately "push" these patients to develop pulmonary edema.

Dr. Rosen asked about those patients who were receiving medications when we did the EEG recording. The serial recordings were done in patients who were not receiving any medication. The acute EEG recordings were performed in patients who were receiving intravenous magnesium sulfate. However, in the previous study we compared the EEG findings in normotensive patients with those in patients with eclampsia, and the other groups were not receiving magnesium sulfate. We still found a marked difference in EEG abnormalities in those who had eclampsia.

With regard to ischemia and pathologic findings and the possibility of hemorrhage, most of what we know about eclampsia at the present time comes from patients who died of eclampsia. As I said, we are still limited in the type of evaluation we can do on these patients.

Recently some authors were recommending all of these invasive investigative procedures for patients who have eclampsia to gain an understanding of the pathophysiologic features. However, I do not think that we are any closer in understanding why patients have convulsions. So we still believe that computerized tomography should be limited to patients who have atypical eclampsia.

Dr. Robertson wanted to know about the patient who died. This was a patient who was transferred from another hospital at 39 weeks of gestation. She was sent to us by car. She had several convulsions during her transfer. By the time she arrived at our hospital, she had cardiac arrest. We resuscitated her in the parking lot. After she was stabilized, she underwent cesarean section because of fetal distress, with delivery of a live infant who weighed 3090 gm. She developed disseminated intravascular coagulation and coma in the immediate postpartum period. She continued to have seizures. She stayed in the intensive care unit for almost 8 weeks. Ultimately she died. However, the family refused autopsy so we did not really understand what had occurred. The computerized tomographic scan finding was normal.

Cervicography: A preliminary report

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Cervicography is a photographic method to document abnormal cervical lesions. Screening for abnormal cervical lesions, one of the seven proposed purposes for cervicography, was investigated in this study. We evaluated 578 cervigrams obtained from patients with normal cervical cytologic tests. The evaluated cervigrams were placed in one of four categories. Seventy-nine (13.7%) of the patients had normal cervigrams; in 152 (26.4%) the result was unsatisfactory; in 159 (27.5%) the cervigram was technically defective; and in 188 (32.5%) the result was suspicious. One hundred one of the patients with suspicious cervigrams had colposcopic evaluations. In 69 patients colposcopically directed biopsies were done; 14 patients had koilocytotic atypia, seven had grade 1 cervical intraepithelial neoplasia, three had grade 2 cervical intraepithelial neoplasia, and one patient had an invasive cervical carcinoma. Although cervicography has not been proved to be cost effective, it is a method worthy of further evaluation. (AM J OBSTET GYNECOL 1985;152:192-7.)

Key words: Cervicography, cytology, cervical screening, Papanicolaou smear

In the twentieth century, reports began to appear describing methods of detecting early cervical lesions. In 1925, Hinselman first described the principals of colposcopy. In 1928, Schiller reported his iodine staining technique. One of the greatest advances occurred in 1944, with the publication of Trout and Papanicolaou's thesis on cervical cytologic testing. The first report on colposcopy appeared in the American literature in 1966. Each of these tests has the specific function of helping the physician diagnose cervical epithelial abnormalities and, either individually or combined, has helped to significantly decrease the incidence of invasive cervical carcinoma.

Despite these tests women continue to have invasive cervical carcinoma; therefore, there remains room for improvement. The false negative rate for cervical cytologic tests reportedly varies between 2.8% and 45%.[1-5] Also, although colposcopy is an excellent investigative method, considerable time and training are required to become an expert colposcopist. Some colposcopic experts question the ability of practicing gynecologists to maintain their expertise in colposcopy because of a lack of opportunity to perform colposcopy in a sufficient number of patients with in situ, microinvasive, and invasive cervical malignancies.

Cervicography was developed as an answer to these problems. As stated by its originator, Dr. Adolf Stafl,[6] "cervicography allows permanent objective documentation of cervical findings." He has proposed seven uses for cervicography. These include documentation, evaluation, treatment, follow-up, screening, teaching, and research. This study was designed to investigate the value of cervicography in one of these uses, screening for abnormal cervical lesions.

Material and methods

The cerviscope consists of a 35 mm camera body attached to a 50 mm extension ring. The camera body* is equipped with a databack exhibiting a six-digit number, the cervigram number. This number, which pro-

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*The single lens reflex camera used was the Minolta 35 mm Single Lens Reflex CVS-1, Minolta Photographic Company.

vides patient identification, is recorded on a patient log sheet and also appears on each cervigram. A 100 mm macrolens is located between the extension ring and a unique light source consisting of 3 prefocused halogen bulbs and a strobe ring flash. The halogen bulbs are necessary for proper illumination of and focusing on the cervix. The use of fast film (ASA 200) and the strobe ring flash allow the cerviscope to be hand-held for easy operation. To minimize user mistakes, all f stops and focusing rings are secured. Focusing is achieved by moving the cerviscope back and forth until the cervix appears in focus.

The patients are positioned as for a routine pelvic examination and Papanicolaou smear. After the Papanicolaou smear is obtained, 4% acetic acid is applied to the cervix. The cervix is scanned with the cerviscope and a second application of 4% acetic acid is applied, after which the two cervigrams are immediately taken.

Cervicography was introduced to the St. John's Mercy Medical Center Obstetrics and Gynecology Clinics in June, 1983. All pregnant and nonpregnant patients entering the clinic with previous normal cytologic tests had cervicography performed as part of routine pelvic examination. The first 578 cervigrams performed in this institution constitute this study. In an attempt to maintain consistency, the initial 400 cervigrams were reviewed and evaluated first by myself and then independently by Dr. Stafl.

The cervigrams were classified in one of four categories. If the entire transformation zone was visible and no abnormal lesions were present, the cervigram was classified as normal. The cervigram was classified as unsatisfactory if the entire transformation zone was not entirely visible. When an adequate cervigram was not obtained because of either equipment or user mistake, it was classified as technically defective. Finally, when an abnormal cervical epithelial lesion was visible, the cervigram was classified as suspicious.

Those patients having suspicious cervigrams received written notification requesting their return for further evaluation. I performed all follow-up colposcopic examinations to assure adequate quality control. Depending upon the clinical indications, colposcopically directed biopsies, endocervical curettages, or cervical conizations were performed on the patients.

Results

Of the 713 cervigrams I have evaluated, 135 are not included in this study because of the unavailability of the follow-up results. At our institution routine cervicography was performed on 578 patients with negative Papanicolaou smears. A total of 79 (13.6%) of these cervigrams were reported as normal, 152 (26.4%) as unsatisfactory, 159 (27.5%) as technically defective, and 188 (32.5%) as suspicious.

Table I. Technically defective cervigrams (n = 159)

	No. of patients	%
Acetic acid applied incorrectly	48	30.2
Entire cervix not visualized	45	28.3
Underexposed	32	20.1
Overexposed	15	9.4
Out of focus	11	7.0
Other	8	5.0

Table II. Colposcopic biopsies in patients with normal Papanicolaou smears and suspicious cervigrams (n = 69)

Pathologic condition	*No. of patients*	%
Squamous metaplasia	20	29.0
Condyloma acuminatum	5	7.2
Koilocytotic atypia	14	20.3
Cervical intraepithelial neoplasia		
Grade 1	7	10.1
Grade 2	4	4.3
Grade 3	0	0.0
Carcinoma	1	1.4
Cervicitis	12	17.4
Other	6	8.7

Unsatisfactory cervigrams failed to reveal the entire transformation zone. This occurs when the transformation zone extends high up into the endocervical canal and no amount of manipulation by the examiner will expose all of the transformation zone. This condition occurred in older patients and those who had had cervical conization. Technically defective cervigrams resulted from either equipment misuse or equipment failure. The reasons for defective cervigrams are listed in Table I. Of the 188 (32.5%) patients who had suspicious cervigrams, 101 of these patients returned for colposcopic evaluation. This examination was abnormal in 74 patients, normal in 26, and unsatisfactory in one. Sixty-nine of the 74 patients with abnormal colposcopic examinations have had colposcopically directed biopsies. Five patients did not have biopsies performed because of pregnancy. Table II lists the results of these biopsies.

Comment

Dr. Adolf Stafl of the Medical College of Wisconsin began developing cervicography approximately 8 years ago. His first report was published in 1981.[6] His patient population consisted of 296 patients with known abnormal cytologic tests and 404 patients with normal cytologic tests. Cervicography was performed on all pa-

Table III. Comparison of cervicographic evaluations

	Stafl (n = 404)		*Blythe (n = 578)*	
Result	*No. of patients*	*%*	*No. of patients*	*%*
Normal	293	72.5	79	13.6
Unsatisfactory	76	18.8	152	26.4
Suspicious	35	8.7	188	32.5
Technically defective	—	—	159	27.5

Table IV. Comparison of abnormal biopsy results

	Cervical intraepithelial neoplasia				
Series	*Grade 1*	*Grade 2*	*Grade 3*	*Carcinoma*	*%*
Stafl	6	2	1	0	35
Blythe	7	3	0	1	13.5

tients. Colposcopic evaluation was performed and compared with the results of cervicography in the group of 296 patients. A total of 136 of these patients had a colposcopic directed biopsy showing cervical intraepithelial neoplasia or carcinoma. In 124 (91.1%) of these patients, abnormal results were detected by both colposcopy and cervicography. These results encouraged us to investigate cervicography. Table III compares the evaluation results of Dr. Stafl's 404 patients with those of the 578 patients in this study. The difference in patient population may explain the variance of the results shown in Table III.

The inappropriate use of acetic acid was the most frequent reason for a technically defective cervigram. The person performing the procedure either did not apply enough acetic acid or waited too long after the application of acetic acid to take the cervigram. A second user mistake was the inability of the cervicographer to photograph the entire cervix because of a failure to realize that the cerviscope must be held in the vagina rather than in the horizontal axis. The latter position resulted in the lower portion of the cervix being obscured by the lower blade of the vaginal speculum. Another user problem dealt with focusing. Because the focus is fixed, the camera is focused by moving it back and forth until the cervix is in focus. As shown in Table I most of the technical problems were user and not equipment related.

Table II lists the results of the colposcopically directed biopsies. The true relationship between koilocytotic atypia and invasive cervical carcinoma remains to be proved; however some authors are recommending the treatment of these lesions. If this becomes accepted therapy, their identification becomes important. A total of 14.4% of the lesions were classified as cervical intraepithelial neoplasia and their identification was important. One of the patients with a normal cytologic test result and a suspicious cervigram had mosaicism in the transformation zone. The patient returned for colposcopic evaluation as requested. Horizonal abnormal vessels were visible on colposcopy, and a biopsy of this area revealed invasive squamous cell carcinoma. This carcinoma potentially would not have been identified for another year without cervicography; thus this technique is primarily responsible for this patient's early diagnosis and treatment.

Thirty-five (8.6%) of Stafl's 404 patients had suspicious results at colposcopy. Twenty-six of these 35 (74.3%) patients had colposcopically directed biopsies that were abnormal. Seventy-four of our 101 (73.3%) colposcopically evaluated patients had similar results.

The patients with normal Papanicolaou smears but abnormal cervigrams and colposcopically directed biopsies from the two studies are compared in Table IV. In Dr. Stafl's study, nine of the 26 patients with abnormal colposcopically directed biopsies (35%) were diagnosed as having cervical intraepithelial neoplasia compared to 10 of 74 (13.5%) in our study.

The results of this study confirm Stafl's earlier conclusions that cervicography can identify patients with false negative Papanicolaou smears. Although the cost effectiveness of cervicography has not been established, I believe it deserves continued investigation and evaluation.

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Discussion

DR. JOHN E. SAVAGE, Minneapolis, Minnesota. To my knowledge the present report, with the exception of Stafl's[1] original work, is the first large-scale attempt at using cervicographic techniques. Interestingly, some rather bothersome problems were encountered by Dr.

Blythe. The thrust of the paper evaluates a technique to identify the asymptomatic woman with negative cytologic test results. Dr. Blythe rightly compares his findings to Stafl's as he had the first 400 cervigrams independently reviewed by Dr. Stafl.

I would like to briefly discuss three points: First, technical difficulties encountered in the present study; second, the yield and cost-benefit analysis over those of present-day techniques; and third, what are the merits of this technique.

Three hundred ten of 578 cervigrams were not interpretable, representing 53.6% of the total group. Indeed, this is a rather striking difference compared to Dr. Stafl's success with 404 patients presented at the conference on early cervical neoplasia in March, 1981, and subsequently published in *Gynecologic Oncology*.[2] Stafl's unsatisfactory yield in that report was 18.1% with no technical difficulties are well described in his presentation. If a technique is to be useful as a screening tool, it needs to be technically satisfactory and reproducible in others' hands. Most likely these difficulties diminish with experience and I would appreciate Dr. Blythe's comments. If cervicography is to be used in large numbers by the practicing gynecologist or general practitioner, similar problems may well distract from its usefulness.

Of 188 suspicious cervigrams in this report, 101 or 17.4% of the total group of the 578 eventually led to the performance of colposcopy. Abnormal examinations occurred in 13% of the total group. Moderate dysplasia or a less severe condition was present 1.9% of the time; however, one invasive squamous carcinoma was found for a yield of 0.17%. The overall yield in this group with negative cytologic test results was 2.07%. Combining Dr. Stafl's 404 patients and Dr. Blythe's 578 patients, severe dysplasia or more severe lesions were present in 0.4% of the total group. The false positive rate for suspicious cervigrams determined colposcopically by Dr. Blythe was 25.7%. The false negative rate of cervicography in this study is indeterminate. In these days of cost-effective medicine and prepaid health plans, yields of this sort will be scrutinized. If one assumes that a Papanicolaou smear costs $5.00, an office visit $15.00, a cervigram and interpretation $5.50, colposcopy $40.00, and biopsy interpretation $45.00, the total cost of this project excluding patient time and inconvenience was $22,100. The cost of a single positive yield for cervical intraepithelial neoplasia or more severe lesions was $1,841. For the same cost each woman might have been screened on seven occasions with Papanicolaou smears. Even with high false negative rates inherent in Papanicolaou smears, the probability of several false negative results in succession is remarkably small.[3]

In experienced hands cervicography does indeed have merit. The potential as a teaching tool for resident education in colposcopy is obvious.[4-6] The correlation between positive findings at colposcopy and at cervicography is >90%. I would suggest that this is presently the area of greatest applicability. Moreover, in our litigious society, documentation may become more an issue. If so, cervicographic techniques offer high-quality photographic evidence.

In closing I wish to commend Dr. Blythe for his efforts to further evaluate this technique and ask these questions: What follow-up has been given to patients in his study with unsatisfactory or technically defective examinations? Based on his experience, what is the appropriate patient population for this technique? Third, can the technique be modified to include other areas at risk, namely, the vulva and vagina? Should the practicing gynecologist begin using this tool in his office?

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DR. KENNETH L. NOLLER, Rochester, Minnesota. Dr. Blythe has successfully completed and clearly presented a well-thought-out clinical trial of the usefulness of cervicography as a screening tool for the detection of cervical neoplasia. I agree wholeheartedly with his conclusions, namely, that cervicography can detect some cases of cervical neoplasia that are missed by cervical cytologic testing and that the technique deserves further consideration. I have used the instrument and can attest to its reliability and durability. It takes excellent pictures of the uterine cervix; no other instrument of which I am aware comes close to it in this ability. It will certainly be useful to document the status of the cervix prior to outpatient therapy for intraepithelial neoplasia. For those clinicians who are active in teaching, it will allow easy recording of the unusual cervix for display at didactic conferences. Numerous research applications are also possible.

However, it has also been suggested that cervicography might be a useful tool for routine screening to detect the presence of cervical neoplasia. Based on the material just presented by Dr. Blythe and the original publication by Dr. Stafl introducing the technique in 1981, I believe that there are now sufficient data available to conclude that cervicography probably is not a useful screening tool.

In theory, screening refers to the testing of an asymptomatic population in order to detect a certain end point which distinguishes individuals with that characteristic from those without the characteristic. For example, it would be possible to screen for anemia by subjecting an entire population to a hemoglobin determination. Before the screening test was performed,

Table I. Example of expected results of screening cervical cytologic testing of a population of 1000 asymptomatic women*

Cytologic test result	*Cervical neoplasia*		*Total*
	True positive	*True negative*	
Positive	16	<1	17
Negative	4	979	983
Total	20	980	1000

*Assume: 20% false negative rate; <1% false positive rate; 2% neoplasia prevalence in population.

Table II. Screening example: cervical cytologic testing in 1000 women

Test result	*True positive*	*True negative*
Positive	16	1
Negative	4	979

Predictive value (positive) = 16 of 16 + 1 = 0.94. Predictive value (negative) = 979 of 979 + 4 = 0.99.

Table III. Cervicographic screening*

Cervigram	*Disease*		*Total*
	Positive	*Negative*	
Positive	26	75	101
Negative	79		79
Total	?	?	180

Predictive value (positive) 26 of 75 + 26 = 26%.
*Results of Dr. Blythe, 1984.

Table IV. Cervicographic screening* in 328 evaluable cases

Cervigram	*Disease*		*Total*
	Positive	*Negative*	
Positive	26	9	35
Negative	293		293
Total	?	?	328

Predictive value positive = 26 of 26 + 9 = 74%.
*Results of Dr. Stafl, 1981.

some arbitrary number would be chosen (usually a value 2 SD below the mean) and all patients having that characteristic would be considered to have a "positive" result. Those individuals with this characteristic (perhaps a hemoglobin of <11 gm/dl) would then be examined completely to determine which truly had the disease called anemia.

Papanicolaou smear screening works much the same way: An asymptomatic population is identified, a cervical cytologic specimen is taken from each female member of the population (or a random sample), and those with cells meeting the criteria for neoplasia are considered to have a positive result. These women then undergo complete evaluation to determine which of them, in fact, have the disease.

For many reasons, cervical cytologic testing is a nearly perfect screen for cervical cancer. Its false positive rate is <1%. However, its major drawback is the fact that it is often falsely negative. In fact, the false negative rate is usually estimated to be 20%. Using these estimates of accuracy, if a population of 1000 randomly selected women, all asymptomatic for cervical cancer, had cervical cytologic specimens obtained and if the prevalence of cervical neoplasia in the community were 2%, it would be expected that 16 of the 20 actual cases in the sample would be detected the first time the Papanicolaou smear was performed (Table I). On further evaluation these 16 women would all be found to have disease. Four of the cases in the community would be missed the first time a Papanicolaou smear was taken. However, the next time the population was screened, it would be expected that three of these four cases would be identified.

The initial screen would also lead to either none, or at most one, woman having an abnormal smear who did not have the disease. From the example, it can be calculated that when a Papanicolaou smear is abnormal, at least 94% of the time the patient has the disease (Table II). When the test result is normal, the predictive value is better than 99%.

In practice, none of us do screening in our offices. Although we talk about office "Papanicolaou smear screening," this is far from a correct use of the word. The fact that a woman has appeared at an office for a Papanicolaou smear may suggest that she has symptoms of gynecologic disease. Thus a walk-in cohort is greatly skewed toward an overrepresentation of persons with the disease. Even those women who appear at an office for contraceptive counseling are a nonrandom sample with unknown biases. The prevalence of cervical neoplasia in a walk-in cohort is almost certainly higher than in the general population.

If cervical cytologic testing is then the benchmark for screening for this disease, how does cervicography compare? Unfortunately, studies that can completely answer that question have not yet been performed. Cervicography would need to be used in a randomly selected population (not a population of women attending a gynecology clinic), and all of the women with both normal and abnormal cervigrams would have to undergo further evaluation for the detection of disease. Neither Dr. Stafl nor Dr. Blythe performed this type of study. Rather, they both used previously screened, walk-in populations.

In Dr. Blythe's report, cervigrams were obtained in 578 women. Over half of these photographs were technically defective or unsatisfactory. This left 267 cases in which the cervigram was evaluable. Nearly 30% (79) of these were normal and 70% (188) were suspicious. Of the 188 abnormal test results, only 101 women returned for colposcopic evaluation. None of those with negative examinations were examined to determine the false negative rate. Thus it is not possible to determine the predictive value when the test result is normal. However, calculated from Dr. Blythe's study, the predictive value when the test result is abnormal is only 25% (Table III). This suggests that if cervicography were used for screening, three of four women with a suspicious cervigram would undergo further testing and would have no neoplastic disease.

In Dr. Stafl's report of 404 cases of cervicography, only 328 cases were evaluable. While the predictive value of an abnormal examination in Dr. Stafl's report was higher (74%), this still implies that one of every four women referred for further evaluation would not have disease (Table IV).

My conclusion, therefore, is that Dr. Blythe's study presented today and Dr. Stafl's study previously published suggest that cervicography is not a good tool for screening for cervical neoplasia for two reasons: First, there are far too many unsatisfactory examinations. Second, even if the technical difficulties could be overcome, the high false positive rate of cervicography means that far too many women without disease would be referred for further evaluation. A screening procedure must have a minimal false positive rate.

Cervicography may very well be a useful tool for many reasons other than screening. I fully agree that we should continue to investigate the technique so that its proper role might be discovered.

Dr. Joseph C. Scott, Omaha, Nebraska. I have one technical question for Dr. Blythe. Since he is an experienced colposcopist, how much do the absence of binocular vision and the appreciation of depth perception inhibit the interpretation of the cervigram? Second, I hope that he will continue his study just for its educational merits.

Dr. Blythe (Closing). The residents all perform colposcopy, but for some reason they cannot realize that it is important to use enough acetic acid so they have a large number of technically defective cervigrams. Certainly the discussants were correct in pointing that out.

The unsatisfactory cervigrams can be eliminated. The cervix is to be scanned with the cerviscope and then the pictures taken. If the entire transformation zone is not seen and the picture is not taken, the number of unsatisfactory cervigrams will automatically decrease.

So I think this technique can do what Dr. Stafl told us it can do, but it is not something you can just pick up and use. You do have to have some experience, and it does take some time to get used to it.

What did we learn for sure from this? One, the equipment will do what the manufacturer says it will do, and I think all people who have had hands-on experience with it will agree with that.

For that reason, the lack of the binocular vision really does not make a lot of difference. You can see very clearly what you are photographing, but you do not get the depth and the change in power you would get with a colposcope.

I might add, this procedure was never designed or intended to replace colposcopy and should never be used to evaluate a patient with an abnormal Papanicolaou smear.

The second thing we can say it will do is identify abnormal cervical lesions. All of the patients who returned had colposcopically acetowhite or more severe epithelial lesions. The question that arises in our minds and everybody else's is: Is what we were finding important? I think that question remains to be decided, and we have heard quite clearly our discussants' opinions.

The third thing I would say is that it is an excellent educational tool for those who are involved in resident education. We have all of our colposcopes attached to television sets so both the patients and the residents in the clinic have immediate vision of what is being seen. This is still a good educational tool for teaching colposcopy.

Dr. Savage, we really do not have any follow-up on those patients with false negative results.

Is it an appropriate technique in the practicing obstetrician-gynecologist's office at the present time? Only as an investigatory tool. If you want to use it in your office and see what kind of results you get with it, I think that is fine, and I would encourage people to do that, but I think its value for this purpose has not yet been proved.

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Is intraperitoneal dextran 70 safe for routine gynecologic use?

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The routine use of intraperitoneal 32% dextran 70 has been suggested as an adjuvant to prevent postsurgical pelvic adhesions. Two hundred thirty-four women received an antiadhesion regimen consisting of intraperitoneal 32% dextran 70, dexamethasone, and promethazine. Ten women (4%) experienced spontaneous leakage of the dextran–peritoneal fluid mixture through their abdominal incisions. Painless bilateral swelling of the labia was noted in 18 women (8%). Mild abdominal bloating and weight gain of from 2.5 to 11 pounds were common. No anaphylactic reactions, peritonitis, or wound infections were experienced by any woman. Intraperitoneal dextran 70 appears to be a safe, well-tolerated antiadhesion adjuvant for routine use in gynecologic operations. (AM J OBSTET GYNECOL 1985;152:198-204.)

Key words: Dextran 70, postoperative adhesions, infertility, gynecologic surgical procedures

Despite microsurgical equipment, gentle tissue handling, and meticulous approximation of tissue surfaces, reconstructive pelvic surgical procedures for purposes of infertility treatment are often compromised by the postoperative formation of pelvic adhesions. Several antiadhesion regimens utilizing various drugs or adjuvants are now widely used on a routine basis by infertility surgeons. One such adjuvant is dextran 70, which is a water-soluble glucose polymer available as a clear, viscid, nonpyogenic solution of dextran 70 (32% w/v dextran 70) in dextrose (10% w/v). This polysaccharide has an average molecular weight of 70,000 and the fluid is electrolyte free and nonconductive (Hyskon, Pharmacia Inc., Piscataway, New Jersey). Initial evidence for the efficacy of dextran came from the work of Mazuji and Fadhli[1] and Polishuk and Aboulafia,[2] who demonstrated a marked reduction in postoperative adhesion formation in animals with the intraperitoneal use of either dextran 40 or dextran 75. Further animal studies in rabbits, rats, and pigs have confirmed these early observations and have indicated that dextran may be especially effective in preventing new or primary adhesion formation.[3] A recent report from the National Institutes of Health Adhesion Study Group demonstrated a decrease in postoperative adhesion formation to the adnexa, peritoneum, and other pelvic viscera following operations in the dextran-treated groups as compared to the saline solution–treated controls.[4] Similarly, Rosenberg and Board[5] performed a prospective, randomized, double-blind study in which 44 women undergoing infertility-related surgery received either 200 ml of 32% dextran 70 or Ringer's lactate solution. A significant reduction in both primary and secondary adhesion formation was noted in the dextran-treated group at the time of second-look laparoscopy 6 weeks later.

As the use of intraperitoneal dextran 70 becomes increasingly popular with infertility surgeons, further consideration must be given to its routine use in gynecologic operations, especially in cases in which a woman's future reproductive ability is to be protected. Clearly, when women are exposed to laparotomy for purposes of benign ovarian cystectomy, hemorrhagic corpora lutea, or ovarian wedge resection, they experience a considerable risk for the postoperative formation of pelvic adhesions.[6] Unfortunately, these adhesions may subsequently cause infertility and necessitate future attempts at pelvic reconstructive surgery. Yet, coincident with this increased use of intraperitoneal dextran by gynecologic surgeons, either alone or in combination with other adjuvants, comes an increased concern for the serious side effects that may result from the routine use of intraperitoneal dextran.

Anaphylactic reactions to dextran have been frequently reported but have dealt with cases in which dextran was administered intravenously.[7] One exception, reported by Borten et al.,[8] described a recurrent anaphylactic reaction following the instillation of 300 ml of 6% dextran 75 intraperitoneally. A pseudo Meig's syndrome has also been reported by Adoni et al.[9] in women following the intraperitoneal use of 400 to 500 ml of 10% dextran 40. Twelve of 25 women in this report experienced postoperative pleural effusion documented by chest radiographs. Complications from the

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use of intraperitoneal dextran have been reported also from a theoretical as well as actual perspective. Bernstein et al.[10] demonstrated that dextran 70 can significantly stimulate bacterial proliferation in the presence of serum and have suggested that dextran may serve as a potential medium for bacterial growth. The use of dextran in combination with other widely used adjuvants such as dexamethasone and promethazine, which exert antiinflammatory actions, might then lead to an increased rate of pelvic infection and further delay wound healing.

In a previous communication we reported our experience with the use of an antiadhesion regimen utilizing intraperitoneal 32% dextran 70, dexamethasone, and promethazine in regard to its effect on the hypothalamic-pituitary-adrenal axis.[11] It is the purpose of this paper to report our continuing experience with this antiadhesion regimen in regard to the side effects presumably caused by the routine inclusion of intraperitoneal dextran 70 in this regimen.

Material and methods

Two hundred thirty-four consecutive women with primary or secondary infertility undergoing surgical correction of tubal, uterine, or peritoneal abnormalities were prospectively studied. The primary surgeon in each case was the same (D. M. M.). Medical abnormalities included two women with sickle cell–hemoglobin C disease, two women with asthma, and two women with ileostomies previously performed for chronic intestinal disease. Written consent was obtained from each patient after approval of the protocol by the Human Subjects Committee of Wayne State University and Hutzel Hospital.

Subjects received dexamethasone, 20 mg intravenously, and promethazine, 25 mg intramuscularly, with the preoperative sedation. Dexamethasone, 20 mg, and promethazine, 25 mg, were placed into the peritoneal cavity along with 100 to 200 ml of 32% dextran 70 (Hyskon) before closure of the parietal peritoneum. Virtually all patients received 200 ml with the exception of a few whose pelvic cavity could not accommodate the larger volume of dextran. The amount of dextran 70 utilized was not based on the patient's weight or severity of pelvic disease. Dexamethasone, 20 mg intravenously, and promethazine, 25 mg intramuscularly, were administered postoperatively every 4 hours thereafter for 48 hours. Prophylactic antibiotics consisting early in the study of 1 gram of cefoxitin (Mefoxin) or later of 100 mg doxycycline (Vibramycin) were administered intravenously every six or twelve hours respectively. On the morning of the first postoperative day, oral cephalexin (Keflex), 500 mg every 6 hours, or later doxycycline, 100 mg every 12 hours, was administered for an additional 48 hours.

Results

Side effects attributed to the routine use of intraperitoneal 32% dextran 70 occurred in almost all women participating in this study. However, these side effects were generally mild and were most often limited to transient weight gain and abdominal bloating. Drainage of peritoneal fluid through the abdominal incision and marked labial edema also occurred in patients in this study.

Ten women (4%) experienced the spontaneous leakage of what appeared grossly to be a mixture of dextran and peritoneal fluid through their abdominal incisions. In two cases, the drainage began within 6 hours of the completion of the surgical procedure, whereas the drainage did not begin until the first or second postoperative day in the remaining eight cases. Although the flow was enough to necessitate frequent dressing changes, the total amount of fluid was estimated at <60 ml.

Painless bilateral swelling of the labia was experienced by 18 women (8%) following the operation. No prior episode of labial edema had been experienced by any of the affected women. The swelling usually appeared on the second or third postoperative day and in each case had spontaneously resolved by postoperative day 7. In no instance was there found to be any discoloration of the labia or any evidence of hematoma formation or trauma. A complaint voiced by virtually every women treated with dextran was a feeling of mild nongaseous abdominal bloating postoperatively. Weight gains of from 2.5 to 11 pounds from the time of admission to the time of discharge were noted.

Comment

The combined use of intraperitoneal dextran 70, dexamethasone, and promethazine did not significantly influence the rate of serious postoperative complications in this series of 234 consecutive, nonselected patients. Complications directly attributed to the use of intraperitoneal dextran 70 were those of incisional drainage, labial edema, and weight gain. The inclusion of the glucocorticoid dexamethasone might be expected to foster water retention and aggravate weight gain. Yet, it is our belief based on extensive prior experience with a dexamethasone-promethazine–only regimen prior to the inclusion of dextran 70 that it was dextran that was principally responsible for the occurrence of incisional drainage and labial edema. Complications felt to be directly related to the use of dextran 70 were not life-threatening and did not necessitate additional care or extend the hospital stay.

Because dextran is produced from sugar beets, Pfeffer[12] has suggested that some patients who are hypersensitive to sugar beets may have an allergic response to dextran. None of the women in this study demonstrated any evidence of anaphylaxis to intraperitoneally administered dextran 70. Although a severe anaphylactic reaction has been reported following the intraperitoneal use of 6% dextran 75, the expected incidence of such reactions to 32% dextran 70 is unknown.[8] However, the widespread use of 32% dextran 70 as a medium for hysteroscopy has not been complicated by the report of frequent allergic reactions.

Leakage of a mixture of dextran and peritoneal fluid through the abdominal incision occurred in 10 women (4%) and was felt to be related to defects in closure of the parietal peritoneum in those women who experienced drainage within 6 hours of the completion of the operation. The beneficial effects of dextran in preventing adhesion formation may be the result of a dextran-induced alteration in the structure of fibrin, making it more susceptible to degradation by plasmin.[13, 14] Dextran may also in part exert its antiadhesion effect by a mechanical hydroflotation effect as the result of the formation of a limited ascites, which floats mobile tissues and prevents prolonged apposition of raw surfaces.[15] Krinsky et al.[16] reported a case in which 50 ml of 32% dextran 70 was instilled into the peritoneal cavity of a young woman at the time of diagnostic laparoscopy. Twenty-six hours later at laparotomy 255 ml of serosanguineous peritoneal fluid was recovered from this patient's abdomen. This increased volume of peritoneal fluid created by the hyperosmolar dextran was believed to be the wound drainage experienced by some of our patients during the postoperative period. No incision was explored when drainage of fluid was discovered because of the fear of wound contamination and also, more importantly, because of the belief, later confirmed, that the drainage was not related to wound infection, seroma formation, or fascial defect that would later lead to dehiscence. Incisional drains were not used in any of the 213 patients who received a Pfannenstiel incision or in any of the 21 patients who had previously received a midline incision, which we repeated.

Drainage of the dextran–peritoneal fluid mixture ceased spontaneously within 48 hours of its commencement in all but one very obese woman (238 pounds) who experienced spontaneous resolution of flow within 72 hours of onset. Wound care consisted only of observation and dressing changes when necessary during the period of active drainage.

The inclusion of dexamethasone, a potent antiinflammatory agent, and promethazine, an antihistamine that may limit tissue response to trauma, might be expected to delay wound healing. Instead, in no instance was the healing process compromised or prolonged and no delayed postoperative incisional complications occurred.

The prophylactic use of antibiotics has been suggested when intraperitoneal dextran 70 is utilized, since dextran is capable of stimulating and supporting bacterial growth.[10] The use of prophylactic antibiotics may be especially important when drainage of dextran through the abdominal incision occurs, since bacteria may be able to gain entry into the peritoneal cavity via the dextran–peritoneal fluid mixture. Early in the study cephalexin was utilized, however, doxycycline was later adopted in response to the observation of others of the high rate of subclinical chlamydial infection found in women with tubal disease.[3]

Painless bilateral swelling of the labia was noted in 18 women (8%). As dextran is absorbed via the lymphatic vessels, it is possible that the labial edema was secondary to lymphatic obstruction. In each case, the edema was painless and did not interfere in those few instances when hydropertubation or pelvic examination was felt to be necessary. Spontaneous resolution of the labial swelling occurred by the seventh postoperative day in every woman. It is noteworthy, that of the last 66 patients to undergo this protocol, not one developed labial edema postoperatively. This may indicate that factors other than the volume of dextran used, such as individual patient susceptibility or variations in postoperative routine, may predispose to the development of labial edema. The Adhesion Study Group[4] reported an incidence of transient labial edema of 2% (1 of 45) following the use of 250 ml of 32% dextran 70. However, because of the small number of patients treated in that study, it is difficult to compare their incidence of transient labial edema to that found in this present study. As in the case of incisional drainage, preoperative counseling as to the possible occurrence of labial swelling did much to allay apprehension in those women who ultimately did experience this dextran-related side effect. A common postoperative complaint of women treated with intraperitoneal dextran was mild nongaseous bloating and weight gain, although no clinical evidence of ascites or ileus was found. All patients were given a full liquid diet on postoperative day 1 and a regular diet beginning on day 2. Weight gains of from 2.5 to 11 pounds were noted to occur during the postoperative period of hospitalization. Women returned to their preoperative weights and noted the disappearance of bloating within 2 to 3 weeks postoperatively. Potassium supplementation was effected in intravenous fluids because of our previous observation that women receiving dexamethasone may frequently experience hypokalemia.[11]

Clinical evidence of pleural effusion was not found in any of the study patients. Routine postoperative chest radiography was not performed in any patient, and therefore the complete absence of pleural effusion cannot be confirmed. However, by limiting the total volume of dextran to 200 ml, it is unlikely that the dextran-induced increase in peritoneal fluid would be great enough to induce the psuedo Meig's syndrome reported by others using larger volumes of dextran 75.[9]

Unfortunately, it is not yet clear what volume of dextran will prove to be optimal for the prevention of postoperative adhesions. Larger volumes may be beneficial in creating a limited ascites and a hydroflotation effect which may be important in the prevention of adhesions. What is not clear, at this time, is the effect of dextran volume in relation to the amount or efficiency of fibrin degradation. If this effect on fibrin degradation ultimately proves to be more important than hydroflotation, then perhaps smaller volumes of dextran can be utilized effectively. Smaller volumes of dextran may result in fewer side effects such as incisional drainage, labial edema, and weight gain.

In summary, animal and human clinical studies strongly suggest that 32% dextran 70 can help to prevent the formation of postsurgical pelvic adhesions. This study does not provide information as to the effectiveness of dextran, either alone or in combination with other adjuvants, in the prevention of postsurgical adhesions. It does, however, indicate that limited quantities of 32% dextran 70 can be safely instilled into the peritoneal cavity at the time of major abdominal surgery with a low rate of serious side effects. In this study some observed side effects may have been influenced by the use of multiple adjuvants, especially dexamethasone. The utilization of dextran 70 should be strongly considered whenever a pelvic surgeon performs a surgical procedure that may have an impact on a woman's future reproductive potential. Since many of the most commonly performed gynecologic surgical procedures fall into this category, we believe that the judicious use of 32% dextran 70 is today indicated for routine use in many women undergoing gynecologic surgery.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. RUDI ANSBACHER, Ann Arbor, Michigan. The title of this presentation is somewhat misleading. Routine gynecologic use would appear to include all benign surgical procedures for gynecologic conditions, not just those that deal with infertility-type operations. Are the authors truly advocating the routine use of Hyskon for all benign gynecologic procedures?

The authors state that they have observed side effects in almost all of the women who had Hyskon instilled into their abdominal cavities during the surgical procedure. They mention spontaneous leakage in 10 women and swelling of the labia in 18 women and then state that almost all had a nongaseous bloating sensation. Were there any other side effects?

Hyskon is a high–molecular weight dextran composed of a complex polysaccharide which has high viscosity and hyperosmolarity. It coats raw serosal surfaces and abrasions and retards blood clot adherence and fibrinous adhesions by its siliconizing effect, which appears to be antithrombotic.[1] It may have fibrinolytic activity and does produce a transient ascites for 3 to 7 days as the dextran molecules undergo metabolism with a shift of extracellular fluid into the peritoneal cavity.[2] The osmotic gradient created draws in about 2.5 times the volume instilled into the pelvis from the vascular space.[1]

The volume of Hyskon instilled into the peritoneal cavity depends upon the size of the pelvis. An amount sufficient to float the tubes and ovaries and cover the uterus should be used. When one takes the patient out of Trendelenburg position, it appears that only 100 ml of Hyskon in most patients is adequate to float the tubes and ovaries and cover the uterus. At the University of Michigan we have limited the volume of Hyskon instilled into the pelvic cavity to 100 ml. From January, 1982, through June, 1984, 75 women received Hyskon intrapelvically prior to closure of the abdominal wall. We observed some fluid shifts with slight abdominal distention but no leakage of fluid through the wound and no labial edema. The use of steroids and promethazine was discontinued when we began using Hyskon in early 1982. We have encountered no wound or pelvic infections to date.

Could it be that the addition of steroids caused some of the problems they encountered? Can they truly attribute the weight gain noted in the postoperative period to the Hyskon or to the steroid therapy? One side effect in our series, not mentioned in this report, is oliguria caused by the fluid shifts from the vascular space to the intraperitoneal cavity. Fluid imbalances secondary to the intraperitoneal osmotic load appear to be entirely related to the amount of Hyskon used.[3]

Allergic reactions can be related to red-beet allergy.[4] Anaphylaxis has mainly been seen in patients in whom >200 ml of Hyskon had been used.

The authors have not proved the effectiveness of Hyskon for the prevention of postoperative adhesions in their series. Neither have they adequately demonstrated the safety of Hyskon in "routine gynecologic use" unless they limit their definition of the latter to infertility surgery, including operations on the fallopian tube and ovary. Interestingly, the usefulness of Hyskon in preventing pelvic adhesions is still debated. In our series I have seen benefit in approximately 80% of patients but do not have adequate control subjects to formally publish the data. Obviously, what is needed is a prospective randomized control study to adequately determine the effectiveness of Hyskon as an adjunct to prevent pelvic adhesions.

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Dr. Jack S. Gruber, Dayton, Ohio. The authors of this paper asked "Is intraperitoneal Dextran 70 safe for routine gynecological use?" The rationale for use of dextran 70 as an adjuvant to prevent postsurgical pelvic adhesions is supported by a review of the literature. The authors then proceed to cite the low incidence of complications in an antiadhesion regimen that did not consist of dextran 70 alone but is combined with dexamethasone and promethazine. I now have 7 years of experience in the use of this regimen as an adjuvant to prevent postsurgical pelvic adhesions in infertility operations and extended it to routine gynecologic use 4 years ago. I have observed a very similar incidence of postoperative complications but have noticed a smaller percentage of women complaining of labial edema and abdominal bloating. The routine use of only 100 ml of dextran 70 would most likely explain my observation. I agree with the authors that the spontaneous leakage, what appears to be a mixture of dextran and peritoneal fluid, through the abdominal incisions is not a serious problem, but it can be very disturbing; I have had the experience of drainage continuing for longer periods than they observed. I continue selectively draining the extra fascial space in some patients, particularly in the obese patients, to reduce wound separation.

I caution readers of this paper against focusing in on the use of dextran 70 alone as their total pelvic adhesion prophylaxis protocol. I must remind you that these patients were treated with dexamethasone and promethazine prior to, during, and after the operation, as well as coverage with antibiotics. It may well be that the loading dose of dexamethasone prior to the operation would prevent any of the anaphylactic reactions reported with its intravenous use in the literature. Also, I would like to point out that the use of dextran 70 is only one of multiple factors involved in the adhesion prophylaxis protocol of these authors. In addition to the use of dextran 70, dexamethasone, and promethazine, the authors' low incidence of side effects may also be attributed to their selection of patients having an elective operation for infertility and thereby their avoidance of patients with active infectious processes. I suspect they also added many of the other adjuvants used in the prevention of pelvic adhesions, that is, the use of nonreactive suture material, meticulous hemostasis, prophylactic antibiotics beyond the temporary ascites, the use of antiprostaglandins in pain control, reduction in postoperative narcotic doses—sometimes augmented with a TENS (transcutaneous electrical nerve stimulator) unit, early feeding of solid foods to stimulate bowel motility, and operating in a progesterone hormonal milieu, all of which improve our surgical result. The author concludes that the side effects of dextran 70 are low enough that any pelvic surgeon should consider its use when performing a surgical procedure that may affect a woman's future reproductive potential. It has been my observation that for many of these patients the prior pelvic surgeon was not an obstetrician or gynecologist but a general surgeon. It has been very difficult to get these surgeons to modify their choice of suture material for use on reproductive tissue. Before asking them to pick up the dextran 70 and pour it in the abdomen, we must first ask them to lay down their catgut and chromic suture material. In reality, the use of catgut and chromic suture material is a proteinaceous string transplant to man to which many patients react with the formation of severe adhesions. I agree with the authors that the routine use of dextran 70 as an adjuvant in adhesion prophylaxis in elective noninfectious gynecologic surgery should be seriously considered by all pelvic surgeons. But, let us not isolate dextran 70 and consider it as the only factor. It may be the most important single factor in our modern adhesion prophylaxis regimen, but changing a single factor will not give you the results achieved by these authors.

Dr. John H. Mattox, Albuquerque, New Mexico. At our institution we did an in vitro study demonstrating that Hyskon supports magnificently bacterial growth in cultures of *Staphylococcus, Streptococcus,* and *Pseudomonas* organisms and *Escherichia coli.* It supports growth over a 48-hour period of time, which is the critical time to the surgeon. The numbers of the bacteria increase in logarithmic amounts, so there is significant growth.

I personally have some reservations about using the material routinely in the patient undergoing a gynecologic operation, because I think this material has been shown to be effective in preventing adhesions only in specialized circumstances.

One of the other things I would like to mention is that the author is using a very complex regimen in trying to prevent adhesions. On a pharmacologic basis, there is a strong case that promethazine would be helpful. However, it is impossible to show either in animals or humans that this agent is really advantageous when one is trying to evaluate which preparation to use. Rather than compounding the experiment by using several drugs to prevent adhesions, one should evaluate the effectiveness of each agent.

Finally, I would like to ask the authors if they have observed the occurrence of shoulder pain. Shoulder pain has been seen on our service, and in some cases it is extremely extensive and requires an extra day of hospitalization.

Dr. L. Russell Malinak, Houston, Texas. I would like to make two points. In contradistinction to the information that you just heard about in vitro bacteriologic growth, we have found that there was no bacterial growth in Hyskon in a similar in vitro study conducted in collaboration with Dr. Tom Elkins, Department of Obstetrics and Gynecology, University of Tennessee Medical School.

Regarding the volume of Hyskon, we use 200 ml routinely, except in those cases in which the patient is very small.

Dr. Magyar (Closing). The points that the discussants brought up are certainly very helpful. In regard to Dr. Ansbacher's comments, are we truly advocating routine use of Hyskon for all benign gynecologic procedures? No, we are not. However, we are asking you to consider its use in young women of reproductive age, for whom you wish to do everything possible to maintain their reproductive potential. I think these patients are very much like infertility patients, and except in situations where there is acute infection or some other definite contraindication, we would not hesitate to use Hyskon. I do not think that there is a great difference between these patients and young women undergoing benign gynecologic surgery.

We did not limit the use of Hyskon based on age, weight, or any of the other preoperative medical conditions that we encountered.

The majority of our patients are private referral patients. However, we did not use Hyskon selectively, since all patients received this medication. Thus, by comparison, a young woman undergoing benign ovarian cystectomy is, in many respects, very much like the typical infertility patient who we dealt with in this study.

Dr. Ansbacher also asked if there were any other side effects. No, there were not. The side effects that we reported were those that we observed. The one question that I would have in my mind is whether or not any patients developed any degree of pleural effusion. This I cannot reflect on, since we did not perform chest x-ray examination routinely in these patients.

As to the volume of Hyskon used, I do not believe that 100 ml is adequate. With Dr. Malinak's comments in mind, I think the question is whether we are attempting merely to cover or coat the pelvic structures with Hyskon or whether we are trying to create a limited ascites. I think 100 ml would be adequate to coat the pelvis, but I believe we are trying to do more than that and perhaps with added volumes of Hyskon, we do create a more extensive and desirable ascites. There may also be a dose-effectiveness relationship between Hyskon and its effect on fibrin degradation.

There is debate in the literature today concerning the ideal volume of Hyskon to be placed into the peritoneal cavity. Krinsky et al.[1] placed a relatively small amount of dextran (50 ml) into the peritoneal cavity. Twenty-six hours later they examined this woman by laparoscopy and found approximately 255 ml of a mixture of peritoneal fluid and dextran. So, perhaps we are desirous of creating a greater volume of peritoneal fluid or a limited ascites, and this can be better achieved with the 200 ml of dextran that is placed into the peritoneal cavity.

In regard to oliguria, we continued our patients' intravenous therapy until the morning of their second postoperative day. I think discontinuing the intravenous therapy sooner would probably limit weight gain and perhaps would decrease abdominal distention. On the other hand, it might then be expected that there would be a greater incidence of oliguria.

I would agree very much with Dr. Ansbacher that the dexamethasone that we utilized did indeed increase the incidence of weight gain as a result of its fluid-retaining properties.

Dr. Gruber and Dr. Ansbacher made mention of a randomized prospective study. The adhesion study group was an attempt to do this. Unfortunately, even though a number of institutions participated, to date the number of patients studied has been relatively small, and with the varying number of surgeons in that study and the unfortunate use of normal saline solution as the control substance, one must question to some degree their study design.

Dr. Gruber mentioned that labial edema and postoperative wound drainage is very upsetting to the patient, and I would agree with him very much. We are very careful to inform our patients prior to the operation that these side effects may occur. Then if the effects are experienced in the postoperative period, the patient is thus forewarned and generally under these circumstances does very well, both physically and emotionally.

Dr. Mattox referred to shoulder pain. This is something that, of course, we have all seen in instances of hemoperitoneum. We certainly see it after laparoscopy, but it has been our experience that we have not had patients complain of shoulder pain following the use of the intraperitoneal dextran.

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Chorionic villus sampling for first-trimester prenatal diagnosis: Northwestern University Program

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We present our initial experience in developing a chorionic villus sampling program at Northwestern University. In phase 1, we performed chorionic villus sampling in 58 patients prior to elective first-trimester abortion, assessing the reliability and reproducibility of obtaining adequate villus samples and performing cytogenetic analysis by means of both the direct and culture methods. Specimens were categorized according to quality: class I, multiple identifiable villi (n = 20); class II, few villi or villi mixed with decidua (n = 15); class III, no villi (n = 23). There was a positive trend between operator experience, amount of villi obtained, and quality of cytogenetic preparations. In March, 1984, we received Institutional Review Board approval to perform chorionic villus sampling in continuing pregnancies (phase 2). Among the first 20 cases we found two abnormalities (47,XY, + 13; 45,X). The remaining 18 pregnancies were continuing. Recommendations are made for developing a chorionic villus sampling program. (AM J OBSTET GYNECOL 1985;152:204-13.)

Key words: Chorionic villus sampling, genetics, prenatal diagnosis

Amniocentesis is currently the technique most commonly employed for prenatal diagnosis of genetic disorders. Although widely practiced, amniocentesis unfortunately cannot be safely performed prior to 15 to 16 weeks' gestation. Thus fetal diagnosis of chromosomal or biochemical abnormalities can rarely be established prior to 18 weeks' gestation.[1] Couples awaiting results frequently undergo considerable psychological stress. Moreover, if a genetic disorder is detected and the couple elects to terminate the pregnancy, an abortion must be performed well into the second trimester. These circumstances impose greater risks and expense to the woman compared with an outpatient first-trimester abortion.

Chorionic villus sampling for first-trimester prenatal diagnosis has the potential of becoming an attractive alternative to genetic amniocentesis. Prior to becoming a standard, however, considerable caution and monitoring is necessary to establish the accuracy and safety of the procedure. We present here our initial experience in developing technical expertise in chorionic villus sampling and in assessing various laboratory methods (phase 1). Thereafter we shall describe our own early experience in introducing chorionic villus sampling for prenatal diagnosis in continuing pregnancies (phase 2). We shall also provide recommendations for those contemplating initiation of a chorionic villus sampling program.

Material and methods

Phase 1. The objectives of this phase of the study were to (1) assess the quality of cytogenetic preparations as a function of chorionic villus specimen quality and

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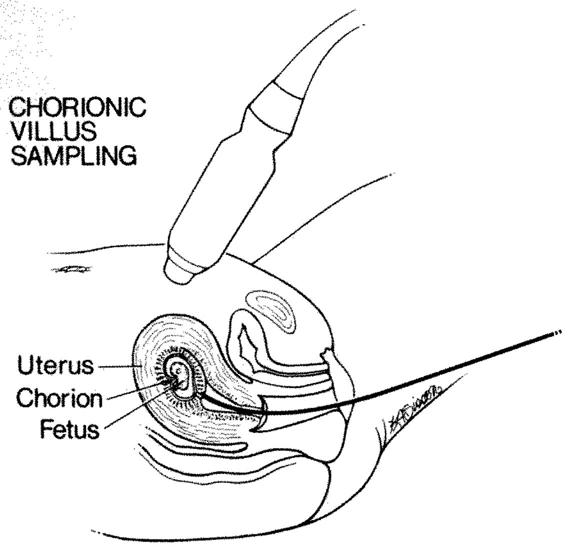

Fig. 1. Chorionic villus sampling procedure.

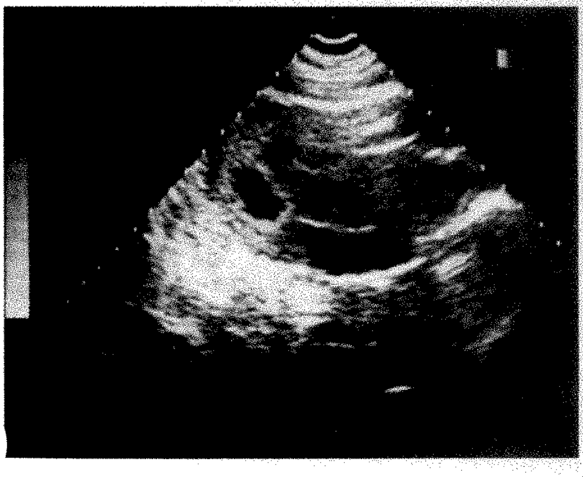

Fig. 2. Ultrasonographic scan (sector transducer, 3.5 MHz) showing chorionic villus sampling catheter approaching chorion frondosum.

Table I. Distribution of the cases in phase 1 of the study according to gestational age as calculated from the beginning of the last menses

Week of gestation	*No. of cases*
6	6
7	8
8	23
9	8
10	8
11	3
12	2

of operator experience, (2) develop laboratory methods for obtaining cytogenetic preparations, and (3) correlate the cytogenetic findings in chorionic villus samples and abortuses.

In August, 1983, our experimental protocol was approved by the Institutional Review Board of Northwestern University, and informed consent of each study subject was obtained. Chorionic villus sampling procedures were performed principally by a single investigator (S. E.) in a series of 58 patients undergoing elective first-trimester (6 to 12 weeks' gestation) abortion. The mean age of these patients was 27.2 years, with a range of 14 to 41 years. The distribution of gestational ages, as determined by the onset of the last menses, is shown in Table I. One of two instruments was used: (1) a 2.4 mm outer diameter, 18 cm long modified pediatric plastic nasogastric feeding tube with two side openings and a blunt tip which has a removable aluminum stylet or (2) a 1.5 mm outer diameter, 21 cm long Portex plastic catheter (Portex, Inc., Wilmington, Massachusetts) which has a removable blunt-ended aluminum stylet that protrudes sufficiently to obliterate the open end. The sampling procedure was performed in a fashion similar to that developed by investigators from London[2, 3] and Milan.[4] To describe briefly, with use of a real-time mechanical sector transducer (3.5 MHz) or a phased-array sector transducer (3.5 MHz), an ultrasound examination was first performed to confirm the gestational age (by measuring the crown-rump length) and to confirm fetal viability (by visualization of heart movements). Patients whose pregnancies were determined to be beyond 13 weeks' gestation or in whom fetal viability was not confirmed were excluded from the study. Under sterile conditions the chorionic villus sampling catheter was then guided transcervically into the substance of the chorion frondosum under continuous ultrasound (sector scan) monitoring (Figs. 1 and 2). After removing the stylet villus material was aspirated into a 20 ml syringe containing 5 ml of Ham's F12 media supplemented with penicillin (100 IU/ml), streptomycin sulfate (50 μg/ml), and heparin (10 IU/ml). No more than four insertions of the catheter were performed in any single patient in attempting to obtain a sample.

Specimens were transported immediately to the laboratory, where they were transferred to Petri dishes and examined under an inverted microscope (× 100). To assess the quality of the specimens, we categorized them into one of three groups: class I, identifiable villi with at least one arborizing cluster; class II, small amounts of villi or mixed tissue, including some villi; class III, unidentifiable tissue, questionable villi, or no villi.

Chorionic villus specimens were processed for cytogenetic analysis in one of two ways: (1) the so-called "direct method" initially described by Simoni et al.[3] and later modified by Gregson and Seabright,[5] or (2) a culture method. In the direct method chromosome preparations are obtained from spontaneous mitoses freed from the cytotrophoblast, which permits cytogenetic

Table II. Proportion of each chorionic villus sampling specimen class as a function of operator experience

Class of specimen	*Chronologic order of cases*					
	1-20		*21-40*		*41-58*	
	n	%	*n*	%	*n*	%
I	6	30	5	25	9	50
II	9	45	5	25	1	5.6
III	5	25	10	50	8	44.4

analysis within 24 to 48 hours. Culturing villi provides a greater number of metaphases and permits cytogenetic analysis in 5 to 7 days.

For the direct method, villi are rinsed in fresh media and minced as necessary. Arborizing clusters of villi are transferred to 35 mm plastic Petri dishes containing 1 ml Chang media (Hana Biologics, Berkeley, California) and maintained at 37° C in an open system (5% carbon dioxide/95% balanced air). Either immediately or after an overnight incubation, cultures are exposed to 1×10^{-6} mol/L concentration of colchicine for 1 to 3 hours. Media are then replaced with a hypotonic solution of 2 ml of 1% sodium citrate for 10 to 15 minutes, rinsed briefly in a 1 : 1 absolute methanol/glacial acetic acid fixative, and stored in a 5:2 fixative overnight at −20° C. Prior to slide preparation the villi are rinsed several times with 5:2 fixative and then treated with 60% to 70% acetic acid for 5 to 10 minutes. Very small drops of the cell suspension are distributed by means of a micropipette onto dry prewarmed slides. The slides are then dried at least 2 hours in an oven at 40° to 45° C. G-banding is achieved by pretreatment with pancreatin and staining with a Wright-Giemsa solution.

In the culture method the villi are washed in Hanks balanced salt solution and transferred to 35 mm Petri dishes containing 3 ml of calcium- and magnesium-free 0.25% trypsin solution; they are then agitated on a girator for 2 hours. The villi and cell suspension are then filtered through a fine wire mesh with use of syringe suction. Villi are removed from the filter, transferred to a 35 mm Petri dish containing 2 ml of calcium- and magnesium-free 0.25% trypsin, and gently agitated for 30 to 60 minutes. Villi are rinsed several times in Chang media and then distributed into 16 ml Flaskettes (Lab-Tek, Miles Scientific, Naperville, Illinois). If necessary, an additional amount of Chang media is added to moisten the growth surface of the Flaskette. Cultures are incubated in an open system (5% carbon dioxide/95% balanced air) at 37° C and monitored daily for growth. When the cultures show adequate mitotic activity (usually 5 to 7 days), they are sequentially exposed to a 2×10^{-7} mol/L concentration of colchicine for 1 to 2 hours, a 0.7% sodium citrate solution for 20 minutes, and several changes of 5:2 absolute methanol/glacial acetic acid fixative. The bottom of the Flaskette (which is a microscope slide) is removed and G-banding is achieved as described for the direct method.

In 10 cases, cytogenetic analyses were performed on the abortuses (methods were a modification of those previously described by Elias et al.[5]) as well as the chorionic villus sampling samples.

Phase 2. Our initial experience (described later) was sufficiently encouraging that in March, 1984, we sought and obtained approval from the Institutional Review Board of Northwestern University to offer chorionic villus sampling in continuing pregnancies. The following were considered to be indications for offering chorionic villus sampling: (1) advanced parental age (usually maternal age of ≥35 years), (2) prior child with a chromosomal abnormality, and (3) fetus at high risk for a detectable mendelian disorder (for example, Tay-Sachs disease, sickle cell disease).

Chorionic villus sampling was performed only in patients whose pregnancies were between 7 and 11 weeks gestation as determined by the onset of the last menses, and confirmed by ultrasonographic measurement of the crown-rump length (that is, between 9 mm and 41 mm). Patients were excluded from the study if (1) fetal viability was not confirmed (by ultrasonographic visualization of fetal heart motion); (2) multiple gestation was diagnosed by ultrasonographic scanning; (3) pathological conditions were present which conferred increased risk in performing chorionic villus sampling (for example, active genital herpes simplex infection, severe cervicitis, active uterine bleeding); (4) large submucous uterine leiomyomas were ultrasonographically visualized, and reasonable access to the chorionic villi was considered impossible.

The techniques for chorionic villus sampling and the processing of specimens were similar to that described in phase 1 except that a 2.1 mm outer diameter radiopaque Teflon catheter (E-Z Cath, Desert Pharmaceutical Co., Inc., Sandy, Utah) cut to 16 cm was used for sampling. Also, the chorionic villus sampling specimens were examined in the operating room under an inverted microscope (×50) to assess the quality of the specimen and the necessity of performing additional samplings. The chorionic villus sampling procedures were performed in an ambulatory surgical suite. Following chorionic villus sampling, fetal heart movements were verified by ultrasonographic visualization.

Because of the uncertain risk of maternal cell contamination in the chorionic villus sampling specimen which could lead to an erroneous fetal diagnosis, the investigative protocol provided the option for each patient whose results showed a 46,XX complement to have a subsequent genetic amniocentesis at no addi-

Table III. Success of culture growth as a function of specimen quality

	Culture growth			
	Growth			
Specimen quality	*n*	*%*	*No growth*	*Total*
I	13	87	2	15
II	1	14	6	7
III	11	69	5	16
Total	25	66	13	38

Table IV. Success of culture growth from class I specimens as a function of laboratory experience

		Successful growth	
	No. of cultures initiated	*n*	*%*
Specimens from Cases 1-30	6	4	67
Specimens from Cases 31-58	9	9	100
Total	15	13	87

tional cost. All patients were scheduled for a follow-up level II ultrasound evaluation at 18 weeks' gestation to survey for gross fetal malformations, particularly neural tube defects, and to assess fetal growth.

Results

Phase 1. In 25 cases the catheter was transcervically passed into the uterus once in an attempt at obtaining chorionic villi, in 25 cases the catheter was passed twice, in seven cases the catheter was passed three times, and in one case the catheter was passed four times. Table II shows that there was a positive trend between the chronologic order of the chorionic villus sampling (that is, increasing operator experience) and an ability to obtain the best quality specimen (class I).

Among 38 specimens in which cultures were initiated from chorionic villi, growth occurred in 66% (Table III). Not surprisingly, the best results (87%) were derived from the 15 cultures initiated from class I specimens. Growth occurred in 67% of cultures initiated from class I specimens obtained during the first 30 cases of the series, but in all class I specimens initiated from the last 28 cases (Table IV). Metaphases showing at least 600 bands were consistently obtained from cultured chorionic villus sampling specimens. Among 39 chorionic villus sampling specimens in which the direct methods were used, we obtained metaphases in 11 (28%); however, the banding quality was not as optimal as that achieved by the culture method.

Among 10 cases in which chromosomal analysis was available from both the chorionic villus sampling specimens and the abortus, there was concordance for sex in 9 of 10 cases. In one class III chorionic villus sampling specimen (poorest quality) the chromosomal complement was 46,XX, but the abortus was 46,XY, indicating maternal cell contamination.

Table V. Summary of chorionic villus sampling procedures in the first 20 diagnostic cases

Case	*Week of gestation*	*Number of passes of chorionic villus sampling catheter*	*Cytogenetic analysis from chorionic villus sampling specimen*
1	11	2	46,XX
2	10.5	2	46,XY
3	9	3	46,XX*
4	10	5	47,XY,+13
5	9	4	46,XX
6	10.5	3	46,XX
7	10	3	46,XX
8	10	3	46,XX
9	8	5	45,X
10	10	3	46,XX
11	10	2	46,XX
12	9.5	2	46,XY
13	8.5	1	46,XX
14	10	2	46,XY
15	7	4	46,XX
16	9	1	46,XY
17	10.5	2	46,XX
18	10	2	46,XX
19	9.5	1	46,XY
20	9.5	3	46,XX

*Amniocentesis at 16 weeks' gestation revealed a 46,XY complement, presumably indicating maternal cell contamination in the chorionic villus sampling specimen.

Phase 2. Among our first 30 women who received formal genetic counseling and were offered chorionic villus sampling, 22 women elected to undergo the procedure. In all except two cases the indications were advanced maternal age (35 years or older). One patient was a 30-year-old woman who had a previous child with trisomy 21, and the other was a 30-year-old woman who had a previous child with trisomy 13. In all cases the fetal heart movement was ultrasonographically visualized, indicating fetal viability. One woman was determined to have a large posterior leiomyoma, and it was believed that access to the chorionic villi would be difficult; chorionic villus sampling was therefore not attempted and the patient was scheduled for an amniocentesis at 16 weeks' gestation. In another woman a twin gestation was ultrasonographically diagnosed, and she was also scheduled for an amniocentesis at 16 weeks' gestation.

The remaining 20 patients underwent the chorionic villus sampling procedure. Table V summarizes the pertinent data. The total amount of chorionic villus sampling specimen per patient ranged from 1 mg to 30 mg as estimated by comparison to a predetermined reference standard in which varying amounts of villi were weighed. In all 20 cases cytogenetic analysis was made by means of the culture method; in 12 of the 20 cases the direct method was also performed. In seven of the 12 direct analysis was believed reliable and indeed the results correlated with that from the culture method. In four of these 12 cases the metaphases were insufficiently spread to permit cytogenetic analysis, whereas no metaphases were observed from one of the cases in which direct preparations were attempted.

Case 4 revealed a 47,XY, + 13 complement and case 9 a 45,X complement. Both patients electively terminated their pregnancies. In case 3 a class III chorionic villus sampling specimen was determined to be 46,XX. We therefore recommended an amniocentesis at 16 weeks' gestation. This revealed a 46,XY complement, presumably indicating maternal cell contamination in the chorionic villus sampling specimen.

Except for the two cases in which patients underwent elective abortion because of a chromosomal abnormality, all pregnancies are currently continuing, (that is, as of October 10, 1984, there had been no spontaneous abortions in our series thus far, with patients having been followed for between 1 and 28 weeks after the chorionic villus sampling procedure). Four patients have experienced spotting per vagina for up to 6 days following chorionic villus sampling. Otherwise, all pregnancies have been uncomplicated.

Comment

Historical aspects. Sampling fetal tissues in the first trimester for prenatal diagnosis was first attempted over a decade ago. In 1973 Kullander and Sandahl[7] studied a series of 39 women undergoing elective pregnancy termination between 8 and 20 weeks of gestation, 25 being between 8 and 12 weeks of gestation. Subjects underwent transcervical chorionic biopsy with use of a 5 mm endocervicoscope and biopsy forceps. Cytogenetic analyses were completed in 20 cases, all of which were normal and concordant with respect to the sex of the abortus. In 19 cases, pregnancy termination was delayed between 7 and 43 days; the only complications consisted of two patients who developed infection.

In 1975 the faculty at Tietung Hospital of Anshan Iron and Steel Company, Anshan, China,[8] reported 100 cases in which pregnancy was allowed to continue after a 3 mm diameter cannula was "blindly" introduced transcervically to aspirate chorionic villi. Fetal sex was determined by X-chromatin analysis. Four pregnancies aborted spontaneously after the procedure, 30 were terminated on the basis of sex prediction, and the remaining 66 pregnancies were allowed to continue. Among these 66 the accuracy rate (that is, correct fetal sex prediction) was 94%.

A different approach was attempted in 1977 by Rhine et al.[9] These workers devised an "antenatal cell extractor" to obtain exfoliated trophoblastic cells by lavage of the lower uterine segment. Unfortunately, our group and others also tried this technique and concluded that first-trimester prenatal diagnosis was not feasible with use of cells obtained by this method.

Improved success for chorionic villus sampling became possible with the development of ultrasound technology that allowed precise placement of sampling devices. In 1982 Kazy et al.[10] in Moscow studied 165 cases between 6 and 12 weeks' gestation. Transcervical chorionic villus sampling was performed in one of two ways: (1) following real-time or gray-scale ultrasonographic evaluation by means of a 1.7 mm diameter fetoscope with a direct-vision biopsy forceps (55 cases) or (2) with use of a 2 mm diameter flexible biopsy forceps under simultaneous real-time ultrasonographic guidance (110 cases). In 26 cases chorionic villus sampling was performed in pregnancies allowed to continue. The indications included hemophilia A or B (14 cases); Duchenne muscular dystrophy (six cases); X-linked hypocephalus (two cases); prior Turner syndrome (four cases). Eleven women elected to terminate their pregnancies because a male fetus was diagnosed; two pregnancies were terminated "at the mother's request." The remaining 13 patients continued their pregnancies. Of these, 11 were delivered of normal infants and two pregnancies were continuing at the time of the report.

In 1982 Old et al.[11] reported 63 patients in whom chorionic villus sampling was performed prior to elective first-trimester abortion (7 to 13 weeks' gestation) via transcervical introduction of a 1.5 mm diameter plastic catheter with a malleable aluminum obturator (Portex Ltd., Hythe, Kent) directed under simultaneous real-time ultrasound guidance. In none of these cases was there any untoward effects following chorionic villus sampling. These investigators then applied similar techniques in three continuing pregnancies. One of two fetuses at risk for β-thalassemia was affected, and the patient elected to terminate the pregnancy. In the other case the fetus was unaffected, and the pregnancy was continued. One case at risk for sickle cell anemia later showed a missed abortion.

In March, 1983, Brambati and Simoni[12] described ultrasonographically directed chorionic villus sampling (Portex catheter) in a 37-year-old woman heterozygous for Duchenne muscular dystrophy. Cytogenetic analysis revealed a 47,XX, + 21 fetus, and the patient elected to terminate her pregnancy. By late spring of 1983 investigators from around the world reported additional case reports and small series describing chorionic villus sampling for first-trimester prenatal diagnosis for a variety of genetic disorders.

The largest reported experience from a single center is from Simoni and colleagues[4] in Milan, Italy. In 1983 they reported 372 cases in which chorionic villus sampling was performed prior to pregnancy termination. In 62 cases the procedure was performed by transcervical fetoscopic sampling, in 159 by blind aspiration of villi by means of a plastic tube, in 48 by blind passage of the Portex catheter, and in 103 by ultrasonographically guided passage of a Portex catheter. In the last series (Portex catheter plus ultrasound studies) the success rate for obtaining villi was 96%. This group utilized a "direct method" to obtain metaphases within hours after chorionic villus sampling. They also assayed eight enzymes directly from villi, thus showing that villi were suitable for rapid diagnosis of metabolic diseases. Subsequently, Simoni et al.[13] reported their first 100 diagnostic chorionic villus sampling procedures in continuing pregnancies, including two sets of twins. In two cases they failed to obtain adequate specimens for analysis. Fetal cytogenetic diagnosis was successful in each of the 96 pregnancies in which fetal material was obtained; in two additional cases villi were not obtained. The abortion rate following chorionic villus sampling was stated to be 8%, and only a few of the pregnancies had been delivered at the time of the publication.

Safety and accuracy. Although numerous groups around the world have now initiated chorionic villus sampling programs, few data are currently available regarding either diagnostic accuracy or safety. There are several potential problems. First, aspirated cells could be of maternal origin (decidua), clearly an issue if the chorionic villus sampling specimen proves to be 46,XX. Fortunately, decidua can usually be distinguished from villi with use of a dissecting microscope; however, potential problems still exist, particularly in inexperienced hands. Second, trophoblastic cells may not necessarily reflect fetal status. Trisomic lines are known to exist in trophoblasts but not in embryonic tissue. Third, in vitro aberrations may arise, as they do in amniotic fluid cells. Overall, substantially more data must become available before assuming that chorionic villus sampling has the same diagnostic accuracy as amniotic fluid culture.

Fourth, and perhaps more troublesome, is the fact that the complication rate as a result of chorionic villus sampling has yet to be established. Of course, any assessment of procedure-related losses must take into account the absolute fetal loss rate as compared to the natural loss rate. Surprisingly, the natural loss rate is unknown. Abortion rates by week of gestation are available, but times of losses in these studies were based on the clinical recognition of fetal death (for example, passage of tissue). However, a fetus could have died weeks prior to the clinical manifestation of spontaneous abortion. Thus the appropriate comparison for chorionic villus sampling studies would be losses occurring in women who show an ultrasonographically viable fetus (that is, a well-defined gestational sac, fetal heart motion, and appropriate crown-rump length) appropriately corresponding to the gestational age as determined by the onset of the last menses. Several sources of data indicate that loss rate after a normal 8 to 10 week ultrasound study is only 2% to 4%, depending upon age and other variables. These sources of data include (1) one prospective collaborative study by our group and others in which pregnancies are diagnosed by β-human chorionic gonadotropin radioimmunoassay within 21 days of conception,[14] and (2) studies in which ultrasonography is routinely performed at the time of initial obstetrical registration.[15] More accurate figures should be available soon. It is apparent, however, that ultragraphically normal pregnancies are thus lost much less often than previously believed. Moreover, losses becoming clinically evident after 8 weeks usually reflect fetal deaths occurring weeks earlier (so-called missed abortions).

Recently, Jackson and Wapner[16] summarized pooled data of diagnostic cases from multiple centers, including our own. Among 1232 registered cases there were 1084 continuing pregnancies (the 148 cases terminated for diagnostic reasons were excluded). None of the 140 infants delivered at the time of the report showed congenital anomalies. In the 1084 pregnancies, 55 (5.1%) of the fetuses were lost for all reasons. In their own experience Jackson and Wapner[16] had only two fetal losses among 170 diagnostic cases. These workers concluded that available data ". . . demonstrate that chorionic villus sampling is safe enough to permit a carefully controlled clinical assessment of its safety and accuracy." Indeed, a prospective and controlled study has been initiated through National Institute of Child Health and Human Development funding. Seven centers in the United States (Baylor Medical School, Jefferson Medical College, Michael Reese Hospital, Mt. Sinai Medical School, Northwestern University, University of California at San Francisco, Yale University) have agreed upon a common protocol in order to assess safety and accuracy. However, it will be several years before definitive data will be available.

Recommendations for introducing chorionic villus sampling as a clinical service. Our initial experience in developing a chorionic villus sampling program at Northwestern University has provided us the basis for making the following recommendations. First, all aspects of chorionic villus sampling performed either before elective pregnancy terminations or for prenatal diagnosis in continuing pregnancies must be under the approval of an Institutional Review Board with informed consent from each subject. Subjects who are candidates for prenatal diagnosis must specifically understand that chorionic villus sampling is investigational and not yet an accepted alternative to genetic amniocentesis. Second, our data in termination cases (phase 1) not surprisingly indicates that the success in obtaining adequate chorionic villi samples and in obtaining accurate cytogenetic analysis is directly correlated with operator and laboratory experience. Accordingly, we concur with the recommendations of Ward et al.[3] in suggesting that the surgical and laboratory methods for chorionic villus sampling should be developed with the help of volunteers undergoing elective first-trimester abortions. Only thereafter should chorionic villus sampling be offered for prenatal diagnosis in continuing pregnancies in which a research protocol is used. Although the number of cases performed on patients prior to elective abortions will vary, we found about 50 cases to be sufficient. Third, in our experience culture methods routinely provide numerous high-quality metaphases (600 bands or greater). However, the direct method has not been so successful in consistently providing high quality metaphases. Modifications of the direct method alone may yet prove sufficient for accurate cytogenetic diagnosis. However, we currently utilize the culture method on all chorionic villus sampling specimens, while also performing the direct method if sufficient material is available. Fourth, we address the potential problem of maternal cell contamination by offering either a repeat chorionic villus sampling or a genetic amniocentesis if the chorionic villus sampling specimen is of poor quality or if only analyses from the culture method are available showing a 46,XX complement. Contamination could yield cytogenetic, biochemical, or DNA restriction endonuclease analyses that are not reflective of the fetal status. If an adequate sample of chorionic villi (≥5 mg) is obtained, the accuracy of prenatal diagnosis is optimized.

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Discussion

DR. FEDERICO G. MARIONA, Detroit, Michigan. The authors have presented a narrative of their tribulations in organizing a clinical program for first-trimester prenatal diagnosis through chorion villi sampling.

They have concomitantly supplied a series of comments that contain a review of the work of other groups worldwide and supported this with 16 references, thus indicating the interest in this technique for the last 11 years.

Any team that has seriously initiated a project of this magnitude must recognize the importance of their recommendations and I fully concur and support those comments.

Our own experience involved the performance of over 100 cases of transcervical chorion aspirations on volunteers undergoing elective first-trimester abortion (8 to 12 weeks); the study was initiated in May, 1983, and protocolized in November, 1983.

Like that of the authors, our phase 1 was designed to assess the safety of chorionic villi aspiration along with the consistency and reliability of ultrasound examination for placental location and catheter guidance and the adequate performance of the cytogenetics laboratory for sample examination, microdissection, and culture techniques. We consider this phase critical in terms of evaluating sample size and cleanliness of the fronds as it related to accurate laboratory determination. Twenty-six such determinations were performed, and except for one culture contaminated with yeast, all villi karyotypes matched the karyotypes obtained from abortion material.

We noticed small differences in the laboratory techniques and realize that they are probably guided by the local experience. Obviously, the purity of the sample, its size, and attention to details increase accuracy and metaphase yield and decrease maternal cell contamination.[1] Our laboratory utilizes both the direct and the culture technique. The decision as to which technique will be used is made at the time of the sampling, since the tissue is observed and evaluated immediately. A very adequate sample (10 mg) will lend itself for direct and culture procedures. A smaller sample is primarily processed for culture, avoiding the waste of valuable material. We extended our study and provided cultured fibroblasts to the biochemical laboratory for enzyme determination.[2] I would like to ask the authors what their experience has been in this regard.

The authors opted for a 2.1 mm diameter catheter for their clinical samples as opposed to continuing with the 1.5 mm catheter used for the cases in phase 1. The catheter was also shorter (16 cm) as opposed to 21 cm in phase 1. In our experience a thicker, shorter catheter that is stiffer introduces easily and may not necessitate a stylet; it obtains a larger but not so clean sample. The lack of standardization of catheters is apparent, since several types are utilized around the world. Our protocol includes presampling and postsampling maternal serum α-fetoprotein determination. Did the authors perform this test? Have they seen any differences? I would like to hear their comments on the value of endocervical cultures obtained prior to sampling, especially in the clinical cases.

I am surprised that of their class III specimens (those called unidentifiable tissue, questionable villi, or no villi) 69% grew. Exactly what is it that grew?

Usually we attempted no more than three catheter insertions, and the maximum in clinical cases has been two. Therefore, I am somewhat concerned that their group attempted five insertions, even though I am aware of the pressure one is under to obtain an adequate sample. Moreover, four of their patients exhibited vaginal spotting for one week; did they correlate this to the number of insertions?

I noticed that in their clinical cases they leaned toward the tenth week (53%) versus 13% in phase 1. Was there any particular reason for this? I definitely agree with their second selection.

Since they established a qualitative classification for their samples, for what reason did they switch to the standard reference we all use (sample weight) for their clinical samples?

The authors discuss the natural embryo loss rate. We have found an unexpected rate of blighted ova and missed abortion at the time of our presample sonographic evaluation. Have the authors any comments? I would like to add that the 0.9% spontaneous loss rate in the National Institute of Child Health and Human Development diabetes study as opposed to the variable rate reported worldwide for chorion villi sampling (0% to 2.8% and 6.5%) requires careful evaluation and clear discussion with the prospective parents.

In summary, by late August, 1984, 2021 women had been sampled worldwide, 1952 of them successfully, and 348 had been delivered. The adjusted loss rate remains at 3.2%.

Chorion villi sampling may demonstrate that its safety and accuracy is equal to or better than that of amniocentesis at 16 weeks, once a randomized, prospective, and controlled study such as the one presently being conducted in Canada, has been completed in the United States (I realize that is easier said than done).

Once these limitations, contraindications, and risks are definitely and properly established and the patients and physicians clearly understand them, chorion villi sampling may offer a distinct advantage in decreasing parental anxiety and maternal morbidity related to advanced second-trimester abortion. Until then, a scientific de minimis approach is strongly recommended.

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Dr. Robert J. Carpenter, Houston, Texas. Within the field of obstetrics, no specific area has changed more rapidly than prenatal diagnosis of fetuses at risk for genetic disease. Currently, chorionic villus sampling is being utilized in multiple centers around the world to obtain first-trimester results in women at risk for genetic disease. The paper under discussion today by Dr. Elias and his colleagues demonstrates in a correct fashion the phases of evaluation which must be utilized by all individuals attempting to do this procedure. One of the most important pieces of information presented by these investigators is that operator efficiency is directly related to extensive preclinical application of this technique. There is a high rate of failed acquisition of adequate specimens for all operators during their initial phase-one procedure, and as they have demonstrated and as seen in our own experience, high-resolution sector scanning is required for defining the location of cord insertion and utilizing it as a marker for insertion of the catheter.

A second factor that is extremely critical in the selection of patients for the procedure and is discussed briefly in their manuscript is the time of gestation. Although the volume of cases is insufficient in continuing pregnancies to demonstrate this, acquisition of specimen is most appropriately reserved for those patients who are at 9 to 11 or 12 weeks' gestation when placental mass and localization can be adequately described by ultrasound scanning to allow passage of the catheter. The two major United States centers with more than 300 cases each have adequately demonstrated this. One center samples only patients of >9 weeks' gestation and has a catheter pass rate of 1.1 insertion per patient, whereas at a second center where 7 and 8 weeks' gestations are routinely sampled, a pass rate of 2.2 per patient is seen in their statistics. Although some may attribute this difference to operator proficiency, both in Dr. Elias's brief experience and in our own, pregnancies at ≥9 weeks' gestation are much easier to sample, with a larger volume of sample recovered and with a higher percentage of class I villi.

In their discussion concerning phase 2 study, multiple issues are raised which require accurate assessment. When these data are available, a reassessment of patients in whom chorionic sampling is appropriate may be required. The major concern for most individuals performing prenatal diagnosis is the overall loss rate intrinsic to chorionic villus sampling, which is above and beyond that of the loss rate at that same gestational age. Only a prospective randomized study stratified for gestational age will provide these data. However, from preliminary attempts by the seven National Institutes of Health centers to initiate this, it appears that patients will often self-select themselves for sampling, which will not result in routine randomization. If this were not the major issue of chorionic villus sampling, one would not be concerned with this patient selection process. However, amniocentesis has a known loss rate of 0.5% (one in 200 patients) in the first 2 weeks following the procedure and can be defined as a safe and accurate procedure. If the loss rate with chorionic villus sampling as seen in the major United States centers with good statistical data is 3%, then women having chorionic villus sampling are at increased risk over those having amniocentesis. Therefore the potential concern as noted by the authors regarding the indications for chorionic villus sampling procedure should be considered carefully. Should the patient at age 35 with a 1% to 2% risk of a chromosomal abnormality be allowed to have chorionic villus sampling in the first trimester when the risk of loss of pregnancy may be at least twice that of her risk for a defective child? Should advanced maternal age for chorionic villus sampling be raised to age 38, 39, or 40? Or should the sampling be reserved for women with high-risk disease such as balanced translocation carriers or metabolic or X-linked disease in which the risk is 25% to 50% and would certainly warrant a 3% loss rate, which is currently the risk for fetoscopy and fetal blood acquisition for hemophilia testing. This is one of several major issues raised by the whole area of chorionic villus sampling. The authors' data with continuing pregnancies will not allow any conclusions to be made. However, their data as well as those of others in the National Institutes of Health collaborative effort and those of our colleagues across the world should be sufficient for this assessment to be made. Other questions that must be answered are (1) What is the risk of prematurity associated with the procedure? (2) What is the risk of intrauterine growth retardation compared to the general population? (3) Will the developmental outcome of the infants in these samplings be any different from that of those for whom sampling was by amniocentesis?

Dr. Elias (Closing). With respect to the first question, our series was limited to cytogenetic analysis. We have not yet performed biochemical analysis on chorionic villus sampling specimens. We are currently initiating such studies with collaborators at Children's Memorial Hospital.

We did not perform α-fetoprotein testing before and after chorionic sampling. This has been considered by other groups. There is some question as to whether the sensitivity for α-fetoprotein testing performed so early in gestation is sufficiently precise to detect any significant changes.

With respect to the question of cervical cultures, we did perform cervical cultures for *Neisseria gonorrhoeae* in many of our patients. However, other groups around the world have recently indicated that the yield from such a screening program is very small.

The issue of whether class III specimens provide diagnostically useful information is indeed a concern. If one gets a 46,XX complement, one would have to seriously consider the possibility of maternal cell contamination (that is, the source of tissue is possibly decidua). On the other hand, we feel that initiation of the culture is very important even if one has a class III specimen because if the results show a 46,XY or a chromosomal abnormality, it would presumably reflect fetal status.

Dr. Mariona expressed concern about our willingness to pass the catheter up to five times. That was only in phase 1 of our study. In continuing pregnancies we limit our number of passages to three.

Another question raised was in regard to the differential between the gestational ages in our phase 1 and phase 2 patients, that is, the phase 1 patients were generally at an earlier gestation compared to patients undergoing diagnostic chorionic villus sampling. The reason was that patients who were in phase 1 were having voluntary interruptions of pregnancy and presented earlier for their interruptions compared to patients undergoing antenatal diagnosis. As Dr. Carpenter had mentioned, our current opinion is that testing between 8 and 10 weeks is optimal.

Dr. Carpenter inquired about the indications for chorionic villus sampling and suggested we consider limiting the procedure to high-risk groups (that is, those at risk for mendelian disorders). In our genetics unit we recommend flexibility in offering patients antenatal diagnosis. We do not adhere to rigid criteria. Each couple must weigh the risks/benefits ratio for themselves in deciding upon chorionic villus sampling or any diagnostic procedure. Finally, current data would suggest that although amniocentesis may ultimately be of less risk with respect to a pregnancy loss as compared to chorionic villus sampling, the surprisingly low spontaneous abortion figures that we have encountered thus far are very encouraging and would, in my opinion, make antenatal diagnosis through chorionic villus sampling a potentially attractive option for indications like advanced maternal age.

Noninvasive prediction of hyaline membrane disease: An optimized classification of sonographic placental maturation

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Accurate prediction of fetal pulmonary maturity by means of a less invasive procedure than amniocentesis would be desirable. Sonographic diagnosis of a Grade III placenta has been reported to be an excellent predictor of fetal lung maturity. The standard classification of placental grading assigns grade according to the most advanced portion of the placenta. Using this classification, we studied 230 patients. In 80 pregnancies with Grade III placenta, three of the neonates developed respiratory distress syndrome. With reclassification of the placentas as immature, (no Grade III areas), intermediate, (only a portion of the placenta being Grade III), or mature, (Grade III placenta throughout), it was found that no neonatal hyaline membrane disease occurred in the 41 pregnancies with mature placentas, whereas 12% of the neonates in the immature group and 8% in the intermediate group developed hyaline membrane disease. These findings suggest that when sonographic examination of the placenta shows both Grade III and non–Grade III sections, there is still a risk for an immature amniotic fluid lecithin/sphingomyelin ratio and neonatal hyaline membrane disease. The placentas should be considered mature only when Grade III changes are present in all sections examined by ultrasound. (AM J OBSTET GYNECOL 1985;152:213-9.)

Key words: Hyaline membrane disease, sonographic placental maturation

Prematurity remains a major cause of perinatal morbidity and mortality. Amniocentesis to assess fetal pulmonary maturity is a widely accepted procedure to predict neonatal outcome. However, it is an invasive procedure associated with morbidity and even fetal mortality.[1] Previous reports have suggested that less invasive methods for predicting hyaline membrane disease might be useful. For example, in a previous study by the authors[2] a sonographically determined fetal biparietal diameter of 90 mm was found to be associated with 100% absence of hyaline membrane disease. Recent advances in ultrasonography have provided the clinicians with the ability to describe the maturational changes in the placenta as pregnancy advances. Grannum et al.[3] assessed sonographically diagnosed placental changes and assigned Grades 0, I, II, and III to the progressively occurring appearance. A Grade III placenta had a perfect correlation with fetal pulmonic maturity. However, this finding was not confirmed by Quinlan et al.,[4] who reported that Grade III placenta could be associated with both an immature lecithin/sphingomyelin ratio and neonatal hyaline membrane disease.

The standard classification of placental grading assigns grade according to the most advanced portion of the placenta[3]; therefore, if Grade III changes are seen in one area of a placenta, the placenta is classified as Grade III. We have recently used this grading system in a study of 230 patients for whom ultrasound studies of the placenta and amniotic fluid phospholipids were evaluated.[5] Among the group of 80 patients who were delivered following a Grade III placenta, three neonates developed hyaline membrane disease. The pur-

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Table I. Modified classification of sonographic placental appearance, which is optimized for prediction of hyaline membrane disease

Modified classification	*Standard classification (Grannum et al.)*
Immature	Grades 0-II, no Grade III
Intermediate	Grade III, part of the placenta only
Mature	Grade III, entire placenta

Table II. Comparison of the modified classification of placental maturation with the standard classification of Grannum et al.

	Standard classification grade			
Modified classification	*0*	*I*	*II*	*III*
Immature (150)	3	19	128	0
Intermediate (39)	0	0	0	39
Mature (41)	0	0	0	41

pose of the present study is to attempt to optimize the classification of placental grading to avoid false predictions of neonatal outcome.

Material and methods

In the study group of 230 high-risk patients referred for fetal maturity assessment, ultrasound examinations were performed at the time of the amniocentesis by two experienced ultrasound technicians who used a linear-array real-time scanner. All sections of the placenta were scanned, and multiple photographic images were made. Initially, one of the authors, blinded to the results of the amniotic fluid tests, evaluated placental grades in all patients with use of the standard placental classification of Grannum et al.[3] in which the grade assigned is that of the most mature area of the placenta visualized. One investigator then reexamined the placental sonographic photographs and reclassified them into a "modified classification system," as outlined in Table I. Placenta was diagnosed as immature when only non–Grade III areas were seen (that is, Grades 0, I, or II according to Grannum's classification), as intermediate placenta when only a portion of the placenta was Grade III and the remaining areas were Grade I or II, and as mature placenta when only Grade III areas were seen throughout all of the sections of the placenta that were examined.

Amniotic fluid was obtained primarily by amniocentesis for clinical indication within 72 hours of delivery. Some of the samples from preterm pregnancies were obtained by needle and syringe through intact membranes at the time of clinically indicated amniotomy. Informed consent was obtained in all cases. The phospholipid profile in the amniotic fluid was determined by means of the two-dimensional thin-layer chromotography technique of Hallman et al.[6] The standardization of this technique in our laboratory has been reported in detail elsewhere.[7] Phosphatidylglycerol was quantitated by scanning the lecithin, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, and phosphatidylserine spots with a transmission densitometer in the dual-beam mode with attached linear recorder and integrator. The densitometer scans of all phospholipids were totaled and phosphatidylglycerol was expressed as a percentage of the total. A phosphatidyglycerol value >2% of the total was considered to be positive.[8]

All patients were evaluated prospectively for an obstetric estimate of gestational age. Infant birth weights and pediatric estimates of gestational age based on the modification by Ballard et al.[9] of the Dubowitz examination were recorded.

One neonatologist, unaware of the sonographic and amniotic fluid findings, evaluated the cause of any respiratory distress on the basis of clinical history, physical examination, and chest x-ray films. The symptoms of respiratory distress used in the evaluation included tachypnea (>60 breaths per minute), cyanosis, grunting, subcostal retractions, and the need for supplemental oxygen in order to maintain Po_2 above 50 mm Hg. The radiologic examinations of the chest were categorized into four grades of hyaline membrane disease. Clinical as well as radiologic manifestations were required to diagnose hyaline membrane disease. Neonates with respiratory distress related to pneumonia, transient tachypnea of the newborn, or congenital heart disease were excluded.

Each category of the modified classification system was examined as to the frequency of each placental grade based on the standard classification system. Patients in each placental maturity grade category of both the standard classification system of Grannum et al.[3] and the modified classification system were examined as to the frequency of hyaline membrane disease, levels of lecithin/sphingomyelin ratio, phosphatidylglycerol, gestational age, and birth weight. The frequencies of pregnancy-induced hypertension and small–for–gestational age neonates were examined in the three categories of patients in the modified classification system. Statistical analysis was performed by means of χ^2; $p < 0.05$ was considered significant.

Results

Clinical risk factors in the 230 patients included repeat cesarean birth, 60 patients; Class A, B, C, or D diabetes mellitus, 34 patients; chronic hypertension, 25

Table III. The association of progressive placental maturity with mean levels of amniotic fluid lecithin/sphingomyelin ratio, percent of phosphatidylglycerol, pediatric estimates of gestational age, birth weight, and frequency of hyaline membrane disease.

Placenta	*Lecithin/ sphingomyelin ratio*	*Phosphatidylglycerol (%)*	*Gestational age (wk)*	*Birth weight (gm)*	*Hyaline membrane disease (%)*
Immature (150)	3.8 ± 1.7	5.0 ± 4.6	37.0 ± 2.7	2788 ± 832	12
Intermediate (39)	4.0 ± 1.5	5.9 ± 4.5	37.7 ± 2.5	2567 ± 863	8
Mature (41)	4.4 ± 1.0	8.2 ± 5.5	39.2 ± 1.6	3133 ± 609	0

patients; severe preeclampsia, 7 patients; suspected intrauterine growth retardation, 46 patients; premature labor, 17 patients; other diagnoses, 41 patients.

The modified classification of placental maturity for patients in this series is compared in Table II to the standard classification of placental maturation introduced by Grannum et al. Of 150 patients with immature placentas based on the modified classification, three patients had Grade 0 placentas, 19 patients had Grade I placentas, and 128 patients had Grade II placentas. Of the 80 patients with Grade III placentas according to the standard system, 39 had intermediate and 41 had mature placentas according to the modified classification.

When placental maturation based on the standard classification of Grannum et al.[3] was related to amniotic fluid phospholipids and neonatal hyaline membrane disease, it was found that all three patients with Grade 0 placentas had lecithin/sphingomyelin ratios <2 and negative phosphatidylglycerol values and had developed hyaline membrane disease. Of the 19 patients with Grade I placentas, five had lecithin/sphingomyelin ratios of <2, 12 had negative phosphatidylglycerol values, and three eventually developed hyaline membrane disease. Of the 128 Grade II placentas, 14 had lecithin/sphingomyelin ratios of <2, 39 had negative phosphatidylglycerol values, and 12 eventually developed hyaline membrane disease. Of the 80 patients with Grade III placentas, four had lecithin/sphingomyelin values of <2, 16 had negative phosphatidylglycerol values, and three developed hyaline membrane disease.

The relationships of placental maturation based on the modified classification with lecithin/sphingomyelin ratio, phosphatidylglycerol values, gestational age, birth weight, and hyaline membrane disease incidence, are shown in Table III. Overall the mean levels of lecithin/sphingomyelin ratio, phosphatidylglycerol, and gestational age were found to increase and the frequency of hyaline membrane disease to decrease as placental maturity advanced. There were three neonates who developed hyaline membrane disease in the group of patients classified as having intermediate placental maturity. All three were the result of pregnancies complicated by chronic hypertension and were delivered prematurely (35, 35, and 36 weeks), based on the pediatric estimates of gestational age. No patients in the mature placental group had an amniotic fluid lecithin/sphingomyelin ratio of <2, negative phosphatidylglycerol value, or a neonate with hyaline membrane disease.

To further understand the basis of this finding, the frequencies of hypertensive disease of pregnancy and small–for–gestational age births were examined in the modified classification system. The mean birth weight in the intermediate group was less than that in either the immature or the mature group. The frequency of small–foræestational age infants was 16 of 39 (41%) in the intermediate group, a significant excess in comparison to 23 of 191 (12%) in the other two groups combined ($\chi^2 = 32.17$, $p < 0.001$). Twenty-one (54%) of the pregnancies in the intermediate group were complicated by severe preeclampsia or chronic hypertension, compared to 34 of 191 (18%) in the other two groups ($\chi^2 = 40.33$, $p < 0.001$).

Comment

The key finding in this study is that a placenta can be considered mature when Grade III maturational changes are present throughout. Thus in order for placental grading to be a reliable predictor of the observed hyaline membrane disease, the Grade III changes, that is, calcifications and the compartmentalizations from the chorionic plate to the basal plate, should be seen in each of its sections. In the present study when the modified classification system was used, a mature placenta was always associated with a mature lecithin/sphingomyelin ratio, positive phosphatidylglycerol value, and absence of hyaline membrane disease in the neonate.

In the standard classification system of placental maturity first described by Grannum et al.,[3] Grade III changes on an ultrasound scanning are only required to be present in one area of the placenta for the appearance to be considered mature. Although the initial study using this definition of Grade III changes showed 100% correlation of Grade III placenta with a mature lecithin/sphingomyelin ratio, findings in subsequent studies have been variable. In a study of normal patients undergoing repeat cesarean birth, Petrucha et al.[10] found that all patients with Grade III placental changes had mature lecithin/sphingomyelin ratios. However, Tabsh[11] found that the lecithin/sphingomyelin ratio was immature in 37% of a group of patients with preterm complications who had Grade III placental changes.

We have previously reported on the relationship of sonographically diagnosed placental maturity to amniotic fluid phospholipid value and neonatal outcome by means of the standard classification system.[5] In the study population sample, a Grade III placenta was associated with 95% mature lecithin/sphingomyelin ratio, 80% positive phosphatidylglycerol, and 96% absence of hyaline membrane disease. In the current study in which the placental ultrasound pictures were reevaluated in patients in whom hyaline membrane disease occurred following identification of a Grade III placenta, it was noted that all of them had Grade III maturity changes only in portion of their placentas. Thus according to the modified classification reported in the present study, these placentas would not be considered mature but would be considered intermediate. This intermediate group of placental maturity was composed largely of pregnancies complicated by maternal hypertensive disease and/or intrauterine growth retardations. This is consistent with previous reports in which sonographic evidence of Grade III placental changes were followed by neonatal hyaline membrane disease in hypertensive mothers.[12, 13] In addition, we have previously reported a significant association of Grade III placenta with intrauterine growth retardation[14]

Multiple studies have shown that progressive placental calcification occurs as gestation advances. Although the mechanism of this calcification is unknown, it has been reported to progress in a predictable fashion and to correlate with fetal maturity. In the present study, pregnancies with Grade III changes present in only a portion of the placenta were more likely to have hypertensive disease or result in the delivery of growth-retarded neonates. One could hypothesize that there may be a different mechanism of placental calcification that results in a Grade III placenta in this group of complicated pregnancies. This mechanism, although unknown, may not be related to fetal maturity.

In the modified classification described in this study, a placenta is considered mature when sonographic changes are seen throughout the entire placenta; if both Grade III and non–Grade III sections are present, there is still a risk for immature amniotic fluid test results and hyaline membrane disease. Moreover, the modified classification described in this study is simple and uses a familiar and straightforward terminology that is descriptive of the neonatal outcome. Although a confirmatory study would be worthwhile, in the author's experience the modified classification is more reliable, since it may avoid the false prediction of hyaline membrane disease which has been a controversial issue with the standard classification.

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Discussion

DR. JAMES P. YOUNGBLOOD, Kansas City, Missouri. Dr. Kazzi and his co-authors are well known for their past work in the use of ultrasonography for prediction of fetal maturity. Last year at this meeting they presented a paper using the biparietal diameter to indicate fetal pulmonic maturity.[1] When the biparietal diameter was >90 mm they had no incidents of infant respiratory distress syndrome.

In the present paper they provide us with a new classification of placental grading which appears to be more accurate in predicting fetal lung maturity than that of the standard Grannum classification. The Grannum classification has been shown to be faulty in that Grade III (mature) placentas have indeed been associated with a small percentage of infants with respiratory distress syndrome. In the authors' group of 230 patients, when the standard classification of placental grading was used, 80 pregnancies had Grade III placentas. Of these 80, three neonates developed respiratory distress syndrome.

The authors' modified classification divides the Grade III placenta classification into intermediate and mature on the basis of either partial or complete changes of placental maturity. The incidence of neonates with respiratory distress syndrome was zero when the entire placenta had Grade III changes throughout. I can find little fault with their final conclusion that placentas should be considered mature only when Grade III changes are present in all sections examined by ultrasound.

It is of interest that the three neonates who developed respiratory distress syndrome and had Grade III placentas by standard classification were in the 35- to 36-week gestational age group and all were electively delivered prematurely from mothers with chronic hypertension. In the modified classification all three infants fell into the intermediate group, and it is also of interest that most of the mothers of the infants in the intermediate group had complications of either hypertension or preeclampsia. These infants also were small for gestational age, and in fact, the intermediate group had a lower mean birth weight than did the immature group. Dr. Kazzi does not state in his paper what percentage of the 41 patients with mature placentas had uncomplicated pregnancies and were more than 38 weeks of gestational age. It has been reported by Quinlan et al.[2] that only 7% of infants at or near term have a mature placenta, as defined in the authors' modified classification. It would appear then that the new classification has its greatest value when a "mature" placenta is present and does indicate almost without exception the presence of fetal lung maturity and, if indicated, whether delivery may be accomplished. In most instances, however, in the group of patients requiring repeat elective cesarean section, one would utilize parameters other than placental grading to make a definitive decision. Such parameters would include serial scanning, femur length, biparietal diameter >90 mm, and even amniocentesis when the other factors are either not reliable or indicate immaturity. To rephrase it: when a mature placenta is diagnosed, amniocentesis may be avoided and delivery may be accomplished.

The authors suggest a confirmatory study as a worthwhile project. It is my opinion that such a study should be prospective, and I look forward to seeing such a study from the authors in the future.

I hasten to add that this modified classification of placental grading with its attendant simplified terminology is a valuable addition to the armamentarium of noninvasive techniques that help diagnose fetal pulmonic maturity.

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DR. RUDY E. SABBAGHA, Chicago, Illinois. In this paper the authors present an original method of defining a mature or Grade III placenta, namely, the ultrasonic appearance of clear-cut cotyledons throughout the placenta rather than in just one portion. However, they do not describe how they can assign specific grades in posteriorly or fundally located placentas. Nonetheless, there is a systematic correlation of placental grade to gestational age, presence of phosphatidylglycerol, birth weight, and hyaline membrane disease.

The authors' initial study[1] of the same group of 230 complicated pregnancies showed that 80 women were considered to have a Grade III placenta by the standard definition. In this group three neonates were reported to have developed hyaline membrane disease and interestingly all were (1) premature, although near term, and (2) the product of pregnancies complicated by chronic hypertensive disease. According to the authors' new definition of Grade III changes, only 41 of 80, or 51%, of these placentas were indeed found to be mature. Further, in each case the pregnancy was beyond 37 weeks, the lecithin/sphingomyelin ratio was >2.0, phosphatidylglycerol was present, and none of the neonates developed hyaline membrane disease. By comparison, the placenta was of intermediate maturity in 39 of 80 (49%) patients. This group encompassed the three previously noted neonates with hyaline membrane disease. Additionally, in this intermediate group there was a statistically significant increase in pregnancy complications and the delivery of small–for–gestational age neonates.

The findings in this report as well as in a variety of other studies indicate that progressive changes in placental grade are related to gestational age, at least in normal pregnancies. The data suggest that it is very unlikely for a neonate to develop hyaline membrane disease in the presence of a Grade III placenta at term.[1, 2] But then, only approximately 15% of such term pregnancies have a Grade III placenta.[3] Thus the clinical utility of the test, that is, a Grade III placenta, is poor. In fact, within this context of a normal pregnancy at term all neonates do pulmonically well regardless of placental grade.[1]

In this study it is not clear how many of the 41 women with a mature placenta (Grade III changes seen in all placenta) were normal. Is it possible that in this group the presence of a mature placenta accurately predicted absence of hyaline membrane disease because the pregnancies were both normal and at term? Regardless of the answer to this question the authors have clarified two areas. First, their new classification of a Grade III placenta appears to be predictive of pulmonary maturity at term. Second, an intermediate placenta is not only associated with hyaline membrane disease but also appears to increase the index of suspicion regarding complications such as intrauterine growth retardation.

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DR. CHIN-CHU LIN, Chicago, Illinois. I enjoyed this paper, its presentation, and discussions. But I want to clarify the point that 8% of the patients with intermediate placenta maturity are associated with hyaline membrane disease and that in fact there is a higher incidence of associated complications of intrauterine growth retardation and hypertensive disorders in this group. Up to now, most people believe that infants with intrauterine growth retardation do not develop respiratory distress syndrome at this maturity. So there is a little contradiction between what is observed and what is thought. Therefore, my first question is, Among the cases with intrauterine growth retardation in which respiratory distress syndrome developed in the intermediate group, are the infants really growth retarded?

I also would like to ask whether the investigators looked at the amount of amniotic fluid as a correlation between oligohydramnios and the placenta maturity or whether they considered it in relation to other parameters in each group.

DR. ROBERT CARPENTER, Houston, Texas. The questions I have concern the 20% of the patients who underwent amniocentesis who were to have elective repeat cesarean section.

I would like to know when the investigators plan a cesarean section? Why did they perform an amniocentesis when the literature suggests that with early ultrasound confirmation of dates, amniocentesis is not necessary if one plans delivery at 39 to 40 weeks? If they excluded their patients having repeat cesarean section from the data, what effect would that have on their results? Also, is there correlation with other patient data, such as incidence of smoking?

We have seen fully mature, entirely Grade III placentas as early as 28 to 29 weeks' gestation in pregnancies with normally developed infants of mothers who smoked two, three, and four packs of cigarettes per day.

DR. RICHARD P. PERKINS, Albuquerque, New Mexico. I want to emphasize a couple of points both of the reviewers have made in relation to the low incidence of Grade III placentas that are found in most populations at this stage of gestation. I wonder what the incidence of the mature placenta as defined by these authors is in their particular population at the gestational age of reference.

We may be talking about such a low-incidence problem or such a low-incidence finding that the presence of it may require a good deal of patience if one is going to wait for it.

Second, if I interpret the data presented by the authors correctly, the incidence of hyaline membrane disease of 8% and 12% in the intermediate and immature groups was associated with the significant frequency of a positive phosphatidylglycerol value. That suggests the possibility of an infant who was initially mature but at the time of delivery may have suffered some sort of metabolic instability that caused a regression of pulmonary maturity behavior; perhaps this is related to the high incidence of perinatal complications in the population that the authors have studied.

I am somewhat puzzled by these findings, since they do not seem to fit precisely with the expectations based on the pulmonary or the phospholipid data.

DR. KAZZI (Closing). We were asked what number of sections of the placenta we were comfortable with. The aim was to have complete visualization of the placenta or as close to complete as possible. In almost all cases the placenta could be examined completely by use of two or three sonographic sections. Early in the study we were using a static scanner to try to get a complete visualization of the placenta. However, we found after comparing static examinations to real-time sonographic examinations that static imaging does not add any more information. However, in about 5% of the patients the placental maturity could not be assessed properly either because of posterior location of the placenta or because of fundal implantation.

Dr. Youngblood asked how many of the 41 patients with mature placentas had uncomplicated pregnancies. The majority (35 of 41) of the pregnancies with mature placentas were normal and uncomplicated. The remaining six had mild obstetric or medical complications, such as gestational diabetes controlled by diet or mild chronic hypertension with no treatment.

Dr. Sabbagha asked how many of the mature placentas were of 38 weeks' gestation or more. Of the 41 pregnancies with mature placentas, two were at 37 weeks and 39 were at ≥38 weeks, according to the Ballard modification of the Dobowitz examination.

Dr. Lin asked whether any of the three neonates with intermediate placental maturity who developed hyaline membrane disease were growth retarded. The answer to this question is no. All three were appropriate in size for gestational age. This does not mean that growth-retarded fetuses do not develop hyaline membrane disease. We have on more than one occasion, seen premature growth-retarded infants develop hyaline membrane disease. Regarding the correlation between amniotic fluid volume and placental maturity, this was not evaluated in the present study.

Dr. Carpenter commented about the high cesarean birth rate and the increased number of amniocenteses in our study. We did not perform amniocentesis in all pregnancies that had previous cesarean deliveries. Whenever early dating criteria were present, such as an ultrasound examination before 20 weeks of gestation, early pregnancy test, and early fetal heart tones by fetoscope, amniocentesis was not performed. These patients were delivered by cesarean section at about 39 weeks. However, most of the patients in the study were indigent and presented for prenatal care late in gestation. In the absence of good dating measurements, one feels obligated to document fetal maturity by amniocentesis. I would like to stress one point: we usually perform amniocentesis and repeat cesarean sections for pregnancies with more than one previous cesarean birth. Those with only one previous low-transverse cesarean birth are usually allowed to labor and deliver vaginally if medical obstetric conditions permit. Regarding the correlation of smoking with placental maturity, this was not addressed in the present study.

Dr. Perkins commented on the low incidence of mature placentas and its real value in detecting fetal maturity. The incidence of Grade III mature placenta varies depending on the population and the definition used. In our original report we had 80 patients with Grade III placentas who constituted 35% of the studied population. If we include only the mature placentas according to the new classification, which would represent 41 patients, the incidence decreased to 18%. Now we have to ask ourselves, "Does this add anything to the management of the patient?" From previous studies, as well as from the study we published before, patients who have mature placentas at term with no complications usually deliver neonates with no respiratory problems. This means that we could have avoided 18% of the amniocentesis procedures if sonographic placental maturation was used to document fetal maturity.

To summarize, I want to say that I believe that there is still a place for sonographically diagnosed placental maturation in the armamentarium of testing for fetal maturity. It can help to avoid the performance of amniocentesis that is associated with some complications.

Erratum

In the article by Naden, Gant, and Rosenfeld, entitled "The pressor response to angiotensin II: The roles of peripheral and cardiac responses in pregnant and nonpregnant sheep," in the February 15, 1984, issue of the JOURNAL, on page 450, some of the values in Table II are incorrect. The correct Table II is shown here.

Table II. Cardiac responses to continuous systemic infusions of angiotensin II

		Rate of infusion of angiotensin II ($\mu g/min$)				
	Control	*0.115*	*0.57*	*1.15*	*2.29*	*11.5*
Heart rate (bpm)						
Nonpregnant	64.9 ± 3.5	64.9 ± 4.0	56.2 ± 3.7*	55.2 ± 3.9*	59.4 ± 3.7	78.2 ± 5.9
Pregnant	103.2 ± 4.4	102.9 ± 3.8	100.2 ± 4.1	94.7 ± 2.6	89.8 ± 3.3†	80.8 ± 3.6*
Stroke volume (ml/beat)						
Nonpregnant	57.5 ± 2.9	56.9 ± 3.2	55.8 ± 3.9	54.3 ± 3.7	51.5 ± 3.5*	45.6 ± 2.9*
Pregnant	69.2 ± 4.1	68.7 ± 4.1	67.1 ± 4.0	66.1 ± 3.2	68.7 ± 3.0	69.5 ± 5.0

Values are mean ± SE (n = 10).

*$p < 0.01$, paired t test, experimental versus control.

†$p < 0.05$, paired t test, experimental versus control.

Office hysteroscopy and suction curettage: Can we eliminate the hospital diagnostic dilatation and curettage?

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The hospital diagnostic dilatation and curettage is the most widely used method in investigating abnormal uterine bleeding. This procedure is expensive and inconvenient and poses some surgical and anesthetic risks. As an alternative to hospital dilatation and curettage, the procedure of office hysteroscopy and suction curettage was evaluated in 406 patients. The indications for the procedure are similar to the classic indications for a diagnostic dilatation and curettage. The method is convenient, safe, and relatively inexpensive. The diagnostic accuracy of office hysteroscopy and suction curettage surpasses prior reports of the accuracy of diagnostic dilatation and curettage. Office hysteroscopy and suction curettage should be the method of choice in the evaluation of abnormal uterine bleeding. (AM J OBSTET GYNECOL 1985;152:220-9.)

Key words: Dilatation and curettage, suction curettage, hysteroscopy, abnormal uterine bleeding

Dilatation and curettage has long been considered the method of choice for investigating abnormal uterine bleeding and for obtaining samples of endometrium for histologic examination. In 1975 approximately 977,000 patients underwent diagnostic dilatation and curettage in short-stay, nonfederal hospitals.[1] This probably makes it the most commonly performed operation in the United States today. Because of the current emphasis on cost containment in health care, there has been increasing motivation to find less expensive procedures to substitute for the routine hospital diagnostic curettage. In addition, a hospital procedure is inconvenient and time consuming. Initially we moved to outpatient procedures instead of the usual 2-day admission. This has reduced costs below what they would have been. However, the increasing costs of hospital operation necessitated raising the charges just for outpatient surgery to very high levels. It is estimated that the average charge for an outpatient dilatation and curettage at Sinai Hospital of Detroit is $960, and to this is added an average anesthesia fee of $100 and a surgeon's fee of approximately $200.

Aspiration curettage without cervical dilatation in an office setting has been shown to be a reliable and acceptable method of endometrial sampling.[1-7] It is, of course, the gynecologist's prime responsibility to rule out endometrial carcinoma and precursor lesions in patients who have abnormal bleeding. However, it is realized by practicing gynecologists that the incidence of carcinoma, especially in younger women, is very low. The primary reason for diagnostic curettage in these patients is to find causes for menstrual abnormalities that can be remedied, such as endometrial polyps and submucous leiomyomas. As the menopause approaches, the incidence of atypical adenomatous hyperplasia and endometrial carcinoma increases. The various studies mentioned above show that aspiration curettage equals and perhaps surpasses conventional dilatation and curettage in its ability to diagnose endometrial carcinoma. Smith et al.,[4] in their study of endometrial carcinoma, thought that the Gravlee jet washer was superior to both curettage and endometrial biopsy as a diagnostic procedure. It is noted in these various studies that on rare occasions the diagnosis of endometrial carcinoma may be missed by all methods previously described.

A large number of symptomatic endometrial polyps and submucous leiomyomas are missed by endometrial biopsy and aspiration curettage. It has long been the gynecologist's view that the conventional dilatation and curettage was more likely to result in the discovery of submucous leiomyomas because one can "feel" with a curette whereas one cannot feel with the usual suction cannula. In addition, in conventional dilatation and curettage, exploration with the polyp forceps will often result in the removal of endometrial polyps which were missed with the curette. It is our impression, on reminiscing on a combined 60 years of gynecologic practice, that many submucous leiomyomas were missed by repeated curettages, that many leiomyomas "found" at curettage were not present at the time of hysterectomy,

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and that many endometrial polyps not discovered at dilatation and curettage were present in hysterectomy specimens when hysterectomy was eventually performed to relieve our patients' symptoms. We do not believe that this experience differs from that of many other experienced gynecologists. MacKenzie and Bibby[2] in a retrospective study of over 1000 diagnostic curettages found that unsuspected pelvic or endometrial lesions were present in 34 of 160 patients who underwent hysterectomy after the initial curettage. Although most gynecologists maintain that dilatation and curettage is by far the most reliable technique for diagnosing endometrial abnormalities, the sensitivity and specificity of a dilatation and curettage are difficult to assess, because unless the uterus is removed, the true incidence of lesions in the uterus is unknown. Stock and Kanbour[8] evaluated the completeness of the curettage performed immediately before hysterectomy. They found that in 60% of the patients, less than half of the uterine cavity was curetted and in 16% of the specimens less than one fourth of the cavity had been curetted. It therefore is not unusual to miss endometrial polyps, submucous myomas, or small endometrial carcinomas at routine curettage. Word et al.[9] demonstrated that 49 of 512 patients who had a hysterectomy following a curettage had residual endometrial polyps. Clearly the curette left many polyps undetected.

Valle has stated: "Hysteroscopy is indicated in any situation in which intrauterine visualization will enhance diagnostic accuracy and define therapy."[10] In our experience the most common indication for hysteroscopy is abnormal uterine bleeding. Because of the nature of our practice, we see a large number of patients with abnormal uterine bleeding that is unrelated to complications of pregnancy. We have gained an extensive experience with hysteroscopy at the time of dilatation and curettage in patients with abnormal bleeding evaluated in the hospital, either as an inpatient or an outpatient.

Material and methods

Since October, 1983, 423 procedures have been performed on 406 patients with abnormal uterine bleeding with use of carbon dioxide hysteroscopy with the Hamou colpomicrohysteroscope or the Wolf hysteroscope. Following hysteroscopy, suction curettage was performed with use of a Novak curette in the first several patients but mostly with a 6 mm flexible suction cannula on a 50 ml syringe. We began using the latter device because we were seeing patients with thicker, succulent endometrium and with endometrial polyps. It was found that the polyps could often be removed with this size cannula. The smaller Novak curette plugged up when a large amount of tissue was present, possibly preventing proper tissue sampling. All patients with abnormal uterine bleeding had endometrial sampling by suction curettage immediately following the hysteroscopy.

Surgical techniques. All hysteroscopies were performed with either the Hamou instrument or a 5 mm hysteroscope. The high-magnification features of the Hamou instrument were not utilized in this study. One author (M. H. G.) routinely uses a paracervical block with 5 ml of 1% mepivacaine into the base of each cardinal ligament because he is of the opinion that the patients are much more comfortable. It is important that one waits at least 2 minutes before beginning the hysteroscopy. This method was used in 372 cases, and the others were performed without anesthesia. There were no untoward effects from the paracervical block.

The patient is placed in the usual position on a regular examination table. Bimanual examination is done to determine the position of the uterus. In our practice we use a Graves speculum. In some cases, a double Sims speculum or other open-sided speculum may facilitate the procedure. The cervix is grasped with a single tooth-tenaculum, and the vagina and cervix are wiped with a solution of Ioprep.

It is helpful and much more comfortable for the operator if the foot of the table is elevated. Most gynecologic examination tables allow this. Carbon dioxide may be delivered through the hysteroscope sheath, with use of one of various types of delivery systems. A simple one is the Kidde insufflator, formerly used for tubal insufflation.[11] The hysteroflator marketed by Karl Storz, Inc., or the Wiest hysteroflator may also be used. *It is imperative that laparoscopic insufflating machines not be used, for these may deliver large amounts of carbon dioxide under pressure and prove disastrous!* A 150 watt light source delivers the light through the fiberoptic cable. This is not adequate for photographic purposes. With a flow rate of 30 to 35 ml of carbon dioxide per minute the hysteroscope is advanced through the endocervical canal. The canal is seen ahead of the scope, and under direct vision the endometrial cavity is entered. The entire cavity is inspected, including the cornual regions, the fundus, the anterior and posterior walls, down to the isthmus. With moderate experience this procedure may take only 30 to 40 seconds. Usually the scope is then removed and a 6 mm flexible suction cannula is inserted. The uterine cavity is aspirated thoroughly by suction while slowly scraping and rotating the cannula over the entire surface of the uterus.

If a lesion is to be sampled, the hysteroscope may be removed and an operating sheath inserted through which small biopsy forceps may be introduced. This is rarely used in our clinical practice.

Table I. Hysteroscopic and/or pathologic diagnosis related to patient age

Hysteroscopic and/or pathologic diagnosis	*21-30 yr (n = 30)*	*31-40 yr (n = 103)*	*41-50 yr (n = 166)*	*51-60 yr (n = 85)*	*61-70 yr (n = 14)*	*71-80 yr (n = 5)*	*81-90 yr (n = 2)*	*91-100 yr (n = 1)*	*Total (n = 406)*
Normal	17	57	84	52	4	3	2	0	219
Submucous myoma	4	23	43	16	1	0	0	0	87
Carcinoma*	0	1	1	4	5	1	0	1	13†
Hyperplasia	0	2	4	5	2	0	0	0	14
Endometrial polyps	2	4	23	7	1	1	0	0	38
Adenomyosis	0	2	1	0	0	0	0	0	3
Miscellaneous and failure of hysteroscopy	7	14	10	1	1	0	0	0	32

*Adenocarcinoma of the endometrium, 12; adenocarcinoma of the cervix, 1.
†Cervix 1.

Table II. Indication for hysteroscopy

Hysteroscopic and/or pathologic diagnosis	*Intermenstrual bleeding (n = 56)*	*Dysfunctional bleeding (n = 54)*	*Postmenopausal bleeding (n = 84)*	*Menorrhagia (n = 149)*	*Menometrorrhagia (n = 23)*	*Other (n = 40)*
Normal (n = 219)	35	34	48	67	12	23
Submucous (n = 87)	5	5	7	59	8	3
Carcinoma (n = 12)	2	0	10	0	0	0
Hyperplasia (n = 14)	3	5	4	1	1	0
Endometrial polyp (n = 38)	10	5	10	11	0	2
Adenomyosis (n = 3)	0	0	0	3	0	0
Miscellaneous* (n = 27)	1	4	1	8	2	11
Failure to complete hysteroscopy (n = 6)	0	1	4	0	0	1
Total	56	54	84	149	23	40

*Synechiae, 14; adenocarcinoma of the cervix, 1; T-shaped uterus in patients exposed to diethylstilbestrol, 4; septate uteri, 4; hemiuterus, 1; imbedded intrauterine device, 2; vascular anomaly, 1.

The patients experience minimal discomfort, which is further decreased by the paracervical block. Only three patients, two with paracervical block, had severe discomfort. In general, the patients have more discomfort from the suction curettage than from the hysteroscopy. Patients are discharged immediately following the procedure. A few patients have shoulder pain because of carbon dioxide passing through the fallopian tubes and rising to the diaphragm. Although gynecologists are aware of this phenomenon, the patients should be warned, since it is often frightening.

Clinical data. Four hundred twenty-three procedures were performed. Some patients received the procedure twice and one patient three times. Their ages ranged from 24 to 94 years. The age distribution of the patients are given in Table I. This age distribution is similar to that of patients having hospital dilatation and curettage. The indications for the hysteroscopy and the suction curettage are noted in Table II. These are the standard indications for dilatation and curettage used by gynecologists for many years. It should be noted that 149 (37%) of the patients were seen for menorrhagia. This reflects the large number of referrals to us because of our interest in laser ablation of the endometrium.[12] Eighty-four of the patients had postmenopausal bleeding or spotting. Ten of these postmenopausal patients had an endometrial carcinoma. One had an adenocarcinoma high in the endocervix. Two patients with intermenstrual spotting also had adenocarcinoma of the endometrium.

Results

The hysteroscopic and/or pathologic diagnoses as related to the presenting symptoms are seen in Table II. In Table I the hysteroscopic and/or pathologic diagnoses are correlated with the patient's age. In addition to the miscellaneous findings unrelated to the patient's symptoms, that is, synechiae, uteri of patients exposed to diethylstilbestrol, septate uteri, and hemiuterus (Table II), significant hysteroscopic diagnoses were made in 181 of the 406 procedures (45%). This is an extremely high diagnostic yield compared to other published reports for diagnostic dilatation and curettage[2] and even more significant when considering the definition we use for normal hysteroscopic and/or pathologic diagnoses. Normal hysteroscopy in this study is defined as the absence of submucous leiomyomas, polyps, or hysteroscopically abnormal endometrium. A large uterine cavity associated with intramural leiomyomas is not considered an abnormal hysteroscopic finding in this study. Atrophic endometrium is considered normal. The presence of minute polyps, which are often seen hysteroscopically, also was considered a normal variant and not significant. Similarly, secretory-appearing endometrium, which is often polypoid, was not considered abnormal. The pathologic diagnosis of "dyshormonal" patterns of the endometrium was also considered normal. This includes the occasional reports of decidual reactions, irregular shedding, and mixed endometrium. Corson and Brooks[11] report significant findings in 64% of their patients with abnormal and/or menopausal bleeding whom they examined hysteroscopically.

The abnormal findings merit further discussion. The most common abnormality seen hysteroscopically in this series was submucous leiomyoma (n = 87). It should be noted that in 28 of these cases there were no palpable myomas on bimanual examination (Table III). In 59 cases palpable myomas were associated with the submucous leiomyoma. In 16 of these, the uterus was larger than that of a 10-week pregnancy. In 43 cases the uterus was less than the 10-week size. Four of these were thought to have adenomyosis. The cases of leiomyomas associated with a normal cavity are also included in Table III and are similarly divided into uteri that were larger or smaller than the size of a 10-week gestation.

Failure to complete the hysteroscopy occurred in six patients. Cervical stenosis was responsible for four cases. Another was the case of a patient with a myoma of greater than 10-week gestational size whose cervical canal was so distorted that the hysteroscope could not be inserted. The sixth was the case of a patient with marked vaginal distortion caused by scarring from a vaginal plastic procedure. In four cases the hysteroscopic examination was considered unsatisfactory because of large amounts of secretory endometrium present. Toward the end of a normal menstrual cycle the profuse amount of succulent secretory endometrium prevents proper examination. These four patients returned after their menstrual period, and in all four a satisfactory examination was accomplished. Hysteroscopic examinations in the proliferative phase of the cycle are strongly advised. The procedure is much more satisfactory in the presence of flattened endometrium, and when performed in the follicular phase of the cycle, it will not interfere with a luteal phase pregnancy.

Of interest was the fact that in five patients the hysteroscopic examination failed to show the submucous myomas previously diagnosed by dilatation and curettage. One of these cases had been previously diagnosed by one of the authors (M. H. G.). MacKenzie and Bibby[2] similarly reported seven "disappearing" leiomyomas in their large series of diagnostic curettages.

Table III. Classification of leiomyomas

Description	*No. of cases*
Submucous leiomyomas without palpable fibroid (adenomyoma 1)	28
Submucous leiomyomas with palpable fibroid	59
Small uterus* (adenomyoma 4)	43
Large uterus†	16
Palpable leiomyomas with normal cavity	48
Small uterus*	
Large cavity	10
Normal size cavity	29
Endometrial polyp	2
Septate uterus	1
Large uterus†	
Large cavity	4
Normal cavity	1
Endometrial polyp	1
Prior submucous leiomyomas diagnosed by curettage but unconfirmed hysteroscopically	5

*Uterus smaller than that of a 10-week gestation.
†Uterus larger than that of a 10-week gestation.

Twelve adenocarcinomas of the endometrium were found for an incidence of 3.0%. This is consistent with the incidence of endometrial carcinoma found by dilatation and curettage in other series. It should be noted that in each of these cases the isthmus and cervix were examined. One showed involvement by carcinoma and was confirmed histologically by hysterectomy. Usually our patients with postmenopausal bleeding have their endocervix curetted separately prior to dilatation and curettage. However, with the presently described technique, fractional curettage probably can be carried out after the hysteroscopic portion of the procedure without risking contamination from endometrial fragments. This should confirm the hysteroscopic impression of presence or absence of cervical involvement which is so important in staging endometrial carcinoma.

To answer the question, "Can we eliminate the hospital diagnostic dilatation and curettage?," we must address the following points: safety, adequacy of specimen and diagnostic accuracy, convenience, discomfort, benefits of examination under anesthesia, and the evaluation of therapeutic effects. These parameters were thoroughly discussed by Grimes[1] in his excellent reappraisal of the diagnostic dilatation and curettage. In an examination of the safety and adequacy of specimens, the Vabra aspiration compared quite favorably with dilatation and curettage. We have every reason to expect that the combination carbon dioxide hysteroscopy and suction curettage will yield similar results.

Lindemann[13] reported no infections in 1500 consecutive carbon dioxide hysteroscopies. Taylor and

Hamou[14] reported no infections in their last 3000 carbon dioxide hysteroscopies. Our series, although considerably smaller, also produced no infections. Similarly, no perforations of the uterus occurred in our series. It seems that the risk of perforation is greater when operative procedures are being performed through the hysteroscope. The technique of passing the hysteroscope through the cervix into the endometrial cavity under direct vision seems to preclude the risk of perforation. Perforation at the time of hysteroscopy seems to be less than at the time of dilatation and curettage.

Grimes,[1] in comparing the diagnostic accuracy of Vabra aspiration versus dilatation and curettage, states that the Vabra aspiration appears to be sensitive in diagnosing adenocarcinoma but less sensitive in detecting polyps. This decreased sensitivity of aspiration curettage to detect polyps can certainly be remedied by the use of carbon dioxide hysteroscopy prior to suction aspiration. In addition, use of a 6 mm suction curette often results in the removal of polyps and negates the necessity of doing a therapeutic curettage. There is no doubt that hysteroscopy reveals many more submucous leiomyomas than does suction curettage or dilatation and curettage. This is evidenced by our finding of 87 submucous leiomyomas. In addition, hysteroscopy should avoid the mistaken "finding" of submucous leiomyomas that are not present.

Hale et al.[5] compared the adequacy of specimens for histopathologic examination by routine dilatation and curettage with flexible suction cannula. They found the suction cannula far superior for adequacy of sampling as well as adequacy of specimen obtained. He also stated that the technique minimizes damage to the basal endometrium and perhaps decreases synechiae.

Though general anesthesia for dilatation and curettage is a safe procedure, there are certainly rare complications associated with it. No complications were associated with the use of paracervical block in this series, and none occurred when the procedure was performed without anesthesia.

The cost of office hysteroscopy combined with suction curettage is compared with an outpatient diagnostic curettage at our institution. As previously stated, the hospital charge for this procedure, including costs of preoperative care, operating room, and postanesthetic recovery room, averages $960. To this is added the anesthesiologist's professional fee of $100, making a total of $1060. To this, of course, we add the gynecologist's professional fee, which I assume would be the same for the office or hospital procedure. The pathologist's fee must also be added. Therefore, over $1000 can be saved per suction dilatation and curettage with hysteroscopy in an office setting as compared to an outpatient hospital procedure. Compared to inpatient hospital procedures, the saving would be even greater.

In assessing convenience, of course, there is no comparison between an office visit and a trip to the hospital, even for outpatient surgery. The procedure, as we described it, is performed during a routine office visit, and it adds about 5 to 10 minutes to the total time of the visit. A trip to the hospital entails at least 1 day of a person's usual routine. If a general anesthetic is used, the patient is often groggy the following day. In addition, she needs someone to accompany her to the hospital and to take her home from the hospital. After office hysteroscopy and suction curettage, our patients leave and drive home themselves with no after-effects from the procedure.

Although examination under anesthesia will occasionally yield findings that are beneficial to the patient, I do not believe they are germane to this discussion. Usually the findings have nothing to do with the reason for the dilatation and curettage. In present-day gynecologic practice there are certainly ample means for the diagnosis of hidden pathologic conditions other than examination under anesthesia, for example, ultrasound studies and computerized tomographic scans.

With regard to the therapeutic effects of diagnostic dilatation and curettage, any direct effect is inconceivable to us unless some pathologic condition is discovered and removed. Grimes[1] is of the same opinion. It is more likely that the improvement of menstrual disturbances following diagnostic curettage is more coincidental than causal. Haynes et al.[15] measured blood loss in women who had a dilatation and curettage for menorrhagia and found that after the first month there was no improvement in the amount of blood loss. This also has been our impression. The combined use of carbon dioxide hysteroscopy and the suction curettage will yield many more cases of endometrial polyps and submucous myomas amenable to proper treatment by therapeutic curettage, myomectomy, or by other appropriate means.

Although hysteroscopy is a new procedure to most gynecologists, its use is proliferating. It is a procedure that is readily learned in a short period of time. It should be taught to residents during their training. Graduate courses in hysteroscopy are available, and it is highly recommended that one be taken by gynecologists who plan to use this procedure. The clarity of the uterine cavity with carbon dioxide hysteroscopy is quite astounding. Most gynecologists are familiar with the appearance of the uterine cavity and its possible contents and therefore readily become secure with hysteroscopic observations. As with most new diagnostic procedures, errors may be made at first; however, ample safeguards are provided by following up with suction curettage in all of these cases.

In conclusion, carbon dioxide hysteroscopy in combination with suction curettage with use of a flexible cannula of 6 mm is a superior alternative to routine dilatation and curettage. At a greatly diminished cost, it provides greater accuracy, convenience, safety, and degree of comfort. Currently it is our primary diagnostic procedure in all patients for whom a dilatation and curettage had previously been indicated. Only in those few instances in which hysteroscopy and suction curettage cannot be completed as an office procedure are we resorting to a hospital procedure, and for these we will add hysteroscopy to curettage under anesthesia.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. ASGHAR AFSARI, West Bloomfield, Michigan. I would like to address my comments in three separate areas: (1) hysteroscopy and its value in the field of gynecology, (2) interpretation of hysteroscopic findings of the endometrium and its pathology, and (3) overall expenses.

The procedure of hysteroscopy had been employed sporadically for many years with limited acceptance, but recent reports that claim more successful and diverse applications have renewed an interest in the procedure.

Looking at the inner cavity of the uterus had always been of interest to many scientists and researchers. An example is the comment of John Clark in 1639, "Seeing is believing."

Hysteroscopy is regarded as the oldest gynecologic endoscopic procedure, which enables us to study the anatomy of the uterine cavity. The history of endoscopy begins in the early years of the nineteenth century (Table I).[1] In 1807 Bozzini constructed a device, called the light conductor, which enabled him to inspect various body cavities. He subsequently was discredited by the Viennese Academy of Medicine. The first hysteroscopy was described in 1869 by Pantaleoni. The patient was 60 years old, with resistant uterine bleeding. Polypoid endometrial growths were observed.

Appropriate to this discussion is the following remark by Jonathon Swift in 1687: "Vision is the art of seeing things invisible." As technologic refinements provided safety and simplicity and clinical experience grew, hysteroscopy became more practical and new applications were developed.

The most common indications for hysteroscopy are as follows: (1) abnormal uterine bleeding, (2) diagnosis and treatment of intrauterine adhesions, (3) missed intrauterine contraceptive device, (4) recurrent pregnancy losses, (5) infertility, (6) diagnosis of endometrial carcinoma and location for possible staging, (7) diagnosis of submucus myoma and removal, (8) diagnosis and removal of endometrial polyps, (9) sterilization, and (10) excision and removal of uterine septum.

The most frequent indication is the evaluation of unexplained abnormal uterine bleeding in premenopausal and postmenopausal patients. Dilation and curettage may not be accurate for diagnosis of focal intrauterine lesions, because they are either small or located in an area difficult to curette. There is a saying attributed to Vauvenargues in 1746 that "Obscurity is the realm of error."

It is stated that even a well-trained gynecologist curettes at best 70% to 80% of the endometrium.[2] Since possibly 20% to 25% of the endometrial surface remains unexplored, one should anticipate the failure rate of some conventional curettage. It was well stated by Publilius Syrus around 43 BC that "Observation, not old age, brings wisdom."

Hysteroscopy can guide the curette and permit targeted biopsy and the direct removal of these lesions. The advantages of performing biopsy under vision rather than by "blind" curettage has been amply demonstrated by many others.

Dysfunctional uterine bleeding by its definition is a form of uterine bleeding unrelated to an organic lesion. This is categorized in Table I of the authors' report. The patients with submucus myoma and endometrial

Table I. Milestones in the development of hysteroscopy[1]

Year	*Investigator*	*Contribution*
1807	Bozzini	First endoscope (light conductor)
1869	Pantaleoni	First hysteroscopic examination in living patient
1879	Nitze	Cystoscope with distal illumination
1907	David	First contact hysteroscope
1914	Heineberg	System for irrigating uterine cavity
1925	Rubin	Use of carbon dioxide for uterine distention
1926	Seymour	Hysteroscope with inflow and outflow channels
1927	Mikulicz-Radecki and Freund	Biopsy-taking capability; cornual electrocoagulation
1928	Gauss	Intrauterine photography
1934	Schroeder	Measurement of intrauterine pressures
1934-1943	Segond	Irrigating systems and biopsies
1936	Schack	Identified applications
1942-1970	Norment	Rubber balloon; practical irrigating system; cutting loops; fiberoptics
1953-1978	Mohri and Mohri	Fiberhysteroscope for intrauterine visualization; tubaloscopy
1957	Englund et al.	Evaluation of abnormal uterine bleeding, comparing hysterography and dilatation and curettage with hysteroscopy
1962	Silander	Study of endometrial carcinoma by means of silicone rubber balloon
1968	Menken	Tubal cannulation; polyvinylpyrrolidone
1970	Edstrom and Fenstrom	Dextran 32%

polyp and the miscellaneous group, however, must not have been included under this heading. Rather, the state of endometrium, that is, proliferative, secretory, or perhaps a mixed pattern, should have been grouped together. Accordingly, the patient group with intermenstrual and dysfunctional uterine bleeding should be added to the category of metrorrhagia for the purpose of simplicity. The impression of dysfunctional uterine bleeding remains as a diagnosis by exclusion, that is, ruling out organic pathologic conditions. Moreover, in this fashion a more diagnostic credibility can be given to the hysteroscopy.

Too often, dilation and curettage fails to detect the source of bleeding, thus subjecting the patient to a disappointing diagnostic procedure. In the case of observing a pathologic entity within the uterine cavity, directed biopsy is preferred. This had been infrequently carried out by the authors. This should also include the endometrial polypectomy under hysteroscopic control. If the removal of the polyp or other lesion is only relied upon by utilizing a 6 mm suction curette attached to a hand-held suction syringe as described by the authors, the procedure then will remain in question, as has been proved in the case of Vabra aspirators by Grimes.[3] Additionally, it is prudent that if the pathologic matter has been removed without direct observation, then an immediate follow-up inspection of the uterine cavity should be carried out by reinserting the hysteroscope for immediate observation. By use of this technique the diagnostic acuity of this procedure will be dramatically improved.

I concur with the authors that, with adequate counseling, most of the outpatient procedures including an office hysteroscopy can safely be performed under local anesthesia. However, for the sake of the patients themselves, as well as the group of patients who are waiting in the waiting room of the office, I personally consider local anesthesia as a preferred method.

I fully agree with the authors about curbing the staggering rise of medical cost; if a measure can be safely employed to reduce some of the unnecessary expenses, it would be very well accepted.

This paper clearly points out that the combination of an office hysteroscopic view of the uterine cavity in conjunction with adequate sampling of the endometrium, excluding the initial cost of the instrument and setting up, not only is able to drastically reduce the cost of a "blind" dilation and curettage, it also can provide a better disposition to be certain about the extent of the endometrial abnormality. There is a quote by Francis Bacon that reads: "If a man will begin with certainties, he shall end with doubts, but if he will be content to begin with doubts, he shall end in certainties" (Advancements of Learning, 1605).

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DR. RAFAEL F. VALLE, Chicago, Illinois. Abnormal uterine bleeding is a common gynecologic problem that prompts women to seek medical attention. Although dilatation and curettage is the traditional method used for obtaining a histopathologic diagnosis, suction biopsy in the office, popularized by Novak,[1] has proved to be a practical and efficient technique for sampling the endometrium. With either method, however, some endometrial pathologic conditions such as polyps and leiomyomas, focal endometrial hyperplasia, or even carcinoma may be undetected.[2, 3]

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*A complete list of references will be provided upon request.

In an effort to improve the diagnostic accuracy of curettage procedures, many physicians now use hysteroscopy to aid in the overall evaluation of the uterine cavity.

In this study Goldrath and Sherman used office hysteroscopy and suction curettage to evaluate 406 patients with abnormal uterine bleeding. A pathologic lesion was diagnosed in 141 patients, including 12 with endometrial adenocarcinomas; 16 patients had endometrial hyperplasia, and 91 patients had submucous leiomyomas.

A major advantage of hysteroscopy is the direct biopsy of any abnormal areas of the endometrium. Therefore the use of hysteroscopy as an adjunct to suction curettage without performing hysteroscopically directed biopsies of abnormal lesions may defeat a primary purpose of hysteroscopy in detecting the presence of focal lesions of the endometrium. This is particularly true in the case of focal lesions located at the uterotubal cones.[4, 5]

Although the diagnosis of submucous leiomyomas and endometrial polyps can readily be made by hysteroscopy in the majority of cases, the accuracy of diagnosing abnormal endometrial conditions by hysteroscopy is as yet unknown. For this reason, directed hysteroscopic biopsies are useful and may obviate the need to repeat endoscopy after curettage to ensure that the abnormal area has been sampled. This is one of the concerns that I have about this approach.

The authors make the case for substitution of hospital dilatation and curettage with office hysteroscopy and suction curettage and cite the relative safety, efficacy, lower cost, decreased morbidity, and convenience. In this study, cost effectiveness for the combined procedure of hysteroscopy and suction curettage was compared to that of the traditional dilatation and curettage performed on an outpatient basis in a hospital setting. A cost reduction of $1000 per patient was achieved by utilization of office facilities. This is most impressive and in keeping with cost-containment efforts being initiated by most insurance plans. The procedure is also appropriate gynecologic care in 1984.

I have a number of questions for the authors.

1. According to the authors, hysteroscopy findings are considered to be normal when submucous leiomyomas or polyps are absent and when the endometrium does not look abnormal. Can they describe "abnormal endometrium" as seen with the hysteroscope? Also, when is suction curettage needed when the endometrium looks normal?

2. How were young patients with a high risk of dysfunctional uterine bleeding of anovulatory origin initially evaluated before being subjected to hysteroscopy and curettage?

3. What was the typical hysteroscopic finding in patients with endometrial hyperplasia and adenocarcinoma of the endometrium? Can the authors offer a topographic description of these hyperplasias and carcinomas? Were the hyperplasias and carcinomas focal or diffuse? Was the diagnosis made hysteroscopically in all cases and were directed biopsies performed prior to suction curettage? If not, how did the authors know that suction curettage had sampled that particular area, since focal lesions might be missed by suction curettage?

4. Was any lesion or pathologic condition missed by hysteroscopy and subsequently diagnosed by suction curettage, or did the opposite occur?

5. Was fractional curettage of the endocervix considered in those patients in whom the endocervical canal appeared hysteroscopically normal?

6. In those cases in which polyps were treated by suction curettage, was a second hysteroscopy performed to ensure that the polyps indeed had been removed?

7. Was the diagnosis of leiomyomas confirmed by hysterectomy, transcervical removal, or biopsy?

8. Was the diagnosis of adenomyosis made by hysteroscopy and/or suction curettage?

Although this study by Goldrath and Sherman demonstrates the cost effectiveness of office procedures for endometrial sampling, the routine addition of hysteroscopy deserves further study. It should also be remembered that the proposed office procedures may not completely eliminate the need for dilatation and curettage in a hospital setting, and as the authors propose, the latter could be reserved for those patients who may not tolerate or are not suitable candidates for office procedures. Nonetheless, the impressive results obtained by the authors support their approach as a good diagnostic alternative in the evaluation of patients with abnormal uterine bleeding, particularly those at high risk for an intrauterine pathologic condition and those with persistent or recurrent symptoms.

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Dr. John J. Barton, Chicago, Illinois. This paper addresses some of the points that Jack Isaacs presented to this society in his paper on endometrial sampling some 4 or 5 years ago. This paper addressses the advantage of hysteroscopy along with endometrial sampling. I am sure it will bring up some of the same questions and some of the lively discussion that followed Isaacs' presentation.

I would like specifically to ask the authors how comfortable they are in staging these endometrial cancers that they are diagnosing.

Dr. Eduard Eichner, Cleveland, Ohio. I want to make a few comments. One is in regard to the use of carbon dioxide in doing the hysteroscopy.

I cannot perform a hysteroscopy because of visual difficulties and so on, but we have seen patients who, while bleeding, received gas in the uterine cavity and had gas emboli. I wonder whether this type of procedure is a satisfactory one and whether hysteroscopies with some of the oil solutions might be more beneficial.

The second comment is that I perform office biopsies routinely on every patient except those in critical emergencies who are going to have a hysterectomy or who have bleeding, and we use the antiprostaglandins to give them emotional relief. If they have any cramping, local anesthesia is given.

We have had no complications or perforation whatsoever, and the biopsies done in this manner have always been verified by the pathology report if the hysterectomy is performed.

In the case of the occasional uterus that is 10, 12, 14 cm in size with irregular bleeding, none of the office instruments are long enough to ensure complete coverage. Or you may find that a large fibroid is partially blocking passage, and you cannot get the hysteroscope or any of the instruments around behind it. What should be done in these cases?

Dr. Philip Flemming, Ann Arbor, Michigan. I have a question for the author. Is the hysteroscope procedure different in the patient who has been sterilized?

Dr. W. Kemp Strother III, Dallas, Texas. Cost effectiveness is one of the key words we have heard this morning; it is something we are all experiencing in our own office and hospital relationship.

If it is not too presumptuous to ask the authors, I would like to know what the local charge for a dilatation and curettage in the area is and what the cost to the patient might be for the procedure according to office activity.

Dr. Gregory J. Feldmeier, Kalamazoo, Michigan. In Kalamazoo we have been performing hysteroscopies for some time. I reviewed 700 of these hysteroscopies, and small polyps were noted frequently as a hysteroscopy finding. The hysteroscopies were performed both for infertility and for abnormal uterine bleeding.

These polyps were not reported by the pathologist as abnormal, and I noted that the authors reported that the small polyps seen by them were considered normal.

I wonder whether the authors felt that, in spite of the small size of those polyps and the normal histologic findings, the polyps were in fact the cause of the infertility or the abnormal uterine bleeding?

Dr. Goldrath (Closing). I will try to close this discussion briefly.

To answer Dr. Afsari's questions, the tables that he mentioned were not presented here because of shortness of time and difficulty of looking at large tables in an audience such as this. We used what would have been the admission diagnosis if the patient were admitted to the hospital. Often we use the terms metrorrhagia, menometrorrhagia, or dysfunctional uterine bleeding. That is how we categorized the indications for the dilatation and curettage.

The removal of polyps was questioned by Dr. Afsari. Yes, if we are removing a polyp with a suction curette we look in immediately afterward to see whether it has been removed. Usually with carbon dioxide hysteroscopy you can see even with some blood in the cavity. If you have difficulty seeing, we have the patient return after another menstrual period and look again. Most of the time we can remove polyps. When polyps are obviously very large, we admit the patient and do a very extensive curettage and exploration with polyp forceps, although we are beginning to do some of these cases in the office.

Dr. Valle brought up the question of directed biopsy. We have been disappointed in directed biopsies. We have not been able to look at endometrium and say that this area is going to have a carcinoma and that this area is going to have hyperplasia.

I think one of the problems we run into with endometrium is that we are looking only at the surface. In looking for abnormalities on the surface, we might say, "Yes, this has a big hump there. It is a polyp," or "This has a yellowish appearance, and that isn't normal," or "This one has a small necrotic area." To pick up views of these small areas may be of interest, but I do not think we can liken it to what we do with colposcopy. Endometrial lesions, as you all know, are really an architectural change in the glandular pattern of the endometrium. Nuclear changes are less important.

Dr. Valle asked what we consider to be an abnormal endometrium. Basically it is what I just alluded to: thickened endometrium, too much endometrium for what we consider the various phases of the cycle. We always do a suction curettage in these patients whether the endometrium looks normal or not. I think that when we are investigating abnormal bleeding, it adds greatly to the procedure. It takes an extra moment. It may cause cramping. As a matter of fact, it does cause a little more cramping than the hysteroscopy, but I think the endometrium should be sampled in all cases.

To answer the question as to what workup the young patients have had before hysteroscopy, basically we have performed hysteroscopic suction curettage for the same indications that all gynecologists use for diagnostic curettage. We do not perform a hysteroscopy or suction curettage in young women who have bleeding unless they have had failure with previous methods of therapy, with which you are all familiar. The procedure is not done as a primary method of investigation in young women. Most of the time we will take a careful history and try the therapeutic approach before we use an invasive procedure on a young woman.

We have talked about the typical findings with endometrial hyperplasia and early carcinoma, and I have great difficulty in telling them apart. I have often looked at the endometrium and said, "This is definitely hyperplastic," and the report will come back as grade 1 adenocarcinoma. I have had many cases that looked like carcinoma but were reported back as hyperplasia. I think that is why we are careful to sample.

Now, where do we go from there? Are we content to say that we have sampled the worst area? No, we are not. If I see an area that looks very suspicious and I get back a totally benign diagnosis, I am going to look again and I am going to sample again. If I find a diagnosis that is not totally benign, as for a patient who has a low-grade carcinoma, of course, she is going to have a hysterectomy, so we have the ultimate biopsy.

Was any lesion or pathologic condition missed by hysteroscopy, and subsequently diagnosed by suction curettage?

Not really—the severity of the lesion might have been missed. The possibility of hyperplasia has been reported back as a low-grade carcinoma, but we did not find lesions in the endometrial sampling from a totally normal-appearing endometrium. I am not saying this is not going to happen, but you get an impression of what a normal endometrium is, and you know when it is abnormal.

The diagnosis of adenomyosis is an interesting one. I think that from a hysteroscopy we can suspect adenomyosis, and then we try to correlate it with the clinical history. I think the suspicion of adenomyosis comes from the myometrium bulging into the endometrial cavity. Normally, the endometrial surface is concave or slightly so, and I believe that in adenomyosis it is convex. It is difficult to make that assumption because we do not do many hysterectomies with a diagnosis of adenomyosis.

Some of the other questions. Dr. Barton asked whether we are comfortable in staging endometrial carcinoma? I think we are as comfortable as we are in staging endometrial carcinoma at any time. It is a difficult staging to do. We are primarily concerned with Stage II carcinomas, of course, and we can look at the endocervical surface. We are covering ourselves by doing endocervical curettage and cervical biopsies in the staging of endometrial carcinomas. I certainly feel much more comfortable doing it this way than with a blind curettage or blind fractional curettage.

Regarding Dr. Eichner's questions about carbon dioxide and gas embolus, this issue has been well studied. You can inject 400 ml of carbon dioxide into the jugular vein of an animal such as a large dog and have no trouble at all. That is a direct injection. Carbon dioxide is highly soluble. We do limit the amounts that we put in or the flow rates, and we are not at all concerned when the patient is bleeding.

If hysterectomy is not performed, we do not, of course, have the specificity of the procedure, but it is certainly an added observation that we can collate in our own personal computers and say, "Look this fits with what we have, and this does not fit with what we have."

Regarding a large uterus, yes, we see an occasional large uterus we cannot fully explore with a hysteroscope but not very many. I think most cases are not referred to us. They are operated on by the physician that originally sees the patient. However, the suction curette will go to a depth of 17 or 18 cm. There are not many uteri that are larger than that.

Dr. Flemming asked about hysteroscopy in a patient with a prior tubal ligation. There is no change at all from that of the patient who has not had a tubal ligation, except that she does not get the shoulder pain.

Dr. Strother, I believe the charge for dilatation and curettage in this area runs between $200 and $300. The office procedure is approximately the same.

Dr. Feldmeier asked about small polyps. I do not have the answer to that, but they are so common that I just cannot pay any attention to them. There are minute polyps that I am sure are just incidental findings. The endometrium does respond to hormonal stimulation in various cycles. I doubt if they are causative of a patient's symptoms or of a patient's infertility.

Erratum

In the December 15, 1984, issue of the JOURNAL, on page 905, Jeffrey P. Phelan, Los Angeles, California, was inadvertently omitted from the list of consultants.

Second-look laparotomy in ovarian cancer: Evaluation of pathologic variables

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From 1977 through 1982, 135 patients with ovarian cancer, having a mean age of 53.7 years and no clinical evidence of disease after approximately 1 year of treatment, underwent a "second-look" laparotomy. Of the 135 patients, 58 (43%) had histologic confirmation of disease at the second-look procedure. Persistent disease was positively correlated with the original stage and negatively correlated with the extent of the original reductive surgery. The original histologic grade or cellular subtype did not significantly influence the findings at reexploration. Patient survival, as judged by percentage of patients alive 3 years after the second-look laparotomy, was dependent on the following surgical/pathologic parameters: tumor size at reexploration, peritoneal cytologic features, residual tumor after reexploration, and histologic grade. (AM J OBSTET GYNECOL 1985;152:230-8.)

Key words: Second-look laparotomy, ovarian cancer, peritoneal cytology, residual neoplasm, histologic grade

The surgical reexploration of patients who successfully completed an initial postoperative adjuvant therapeutic program for ovarian carcinoma has become an integral part of the overall treatment of this disease process. This concept of a "second-look" operation was originally introduced 3½ decades ago by Wangensteen et al.,[1] primarily for assessing the disease status in patients who had undergone exploration for colonic carcinoma. Although Gilbertsen and Wangensteen[2] used similar surgical criteria in the treatment of cancer of the female gonad, the applicability of second-look laparotomy in ovarian carcinoma did not gain momentum until the advent of more effective combination chemotherapy for this neoplasm. Presently, potential benefits of the procedure include (1) avoiding premature discontinuation of therapy when residual, although clinically inapparent, disease is present and (2) terminating chemotherapy as soon as histologic evidence allows, thereby minimizing the acute toxic and potential long-term sequelae of these agents. However, while the diagnostic and therapeutic merits of this approach have generally been endorsed by gynecologic oncologists, the impact of second-look exploration on the overall survival of patients with ovarian cancer is at best difficult to assess. Presumably, retrospective evaluation of various surgical and pathologic variables recorded at primary laparotomy and at subsequent exploration might result in better selection of candidates for second-look procedures (particularly among patients with localized disease), identify therapeutic criteria (resulting in enhanced regression rates with advanced disease), and predict optimal conditions for various modes of salvage therapy after positive second-look operations. We evaluated whether various surgical/pathologic parameters recorded at primary operation influenced the results observed at second-look operation and assessed the influence of several surgical/pathologic parameters at the second-look procedure on subsequent survival.

Methods

The records of 135 patients who had undergone primary surgical treatment and reexploration after attaining or maintaining a clinical status of no apparent disease between January 1, 1977, and December 31, 1982, were reviewed. Definitive primary staging and tumor reductive surgical procedures were performed at our institution in 64 patients (47%). The accompanying operative reports in the referred population adequately documented (1) the extent of neoplasm for accurate staging and (2) optimal tumor debulking in 56 cases (41%), with 15 patients (11%) undergoing a second operative procedure to accomplish these goals.

Postoperative adjunctive therapy was individualized on the basis of stage, extent of tumor reduction, and histologic grade. Therapy ranged from observation only (4%) in Stage IAi or IBi and grade 1 disease to multiagent chemotherapy in advanced disease. Chemotherapy was used in 87% of the patients. This involved either L-phenylalanine mustard or cyclo-

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From the Mayo Clinic and Mayo Foundation.

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Table I. Perioperative morbidity in 135 cases of second-look laparotomy

Morbidity	Patients	
	No.	%
Urinary tract infection	5	3.7
Ileus (prolonged)	3	2.2
Wound infection	3	2.2
Other*	4	3.0
Total	15	11.1

*Pelvic lymphocyst, pseudomembranous colitis, preoperative transfusion reaction, and sheared subclavian catheter.

Table II. Relationship of disease status at second-look laparotomy to original surgical stage in 135 cases

Original Stage	No. of patients	Negative reexplorations*	
		No.	%
I	35	30	86
II	22	17	77
III and IV	77	29	38
Unknown	1	1	100
Total	135	77	57

*Absence of macroscopic or microscopic disease.

Table III. Relationship of disease status at second-look laparotomy to original histologic cell subtype in 135 cases

Original histologic type	No. of patients	Negative reexplorations*	
		No.	%
Mucinous	20	16	80
Endometrioid	12	8	67
Clear cell	6	4	67
Serous	79	40	51
Adenomatous†	13	5	39
Other	5	4	80
Total	135	77	57

*Absence of macroscopic or microscopic disease.
†Histology not otherwise specified.

Table IV. Relationship of disease status at second-look laparotomy to original histologic grade

Original grade	No. of patients	Negative reexplorations*	
		No.	%
1	30	22	73
2	31	19	61
3	50	21	42
4	23	15	65
Unknown	1	0	0
Total	135	77	57

*Absence of macroscopic or microscopic disease.

phosphamide when single agents were chosen or cyclophosphamide in combination with cisplatin, doxorubicin, and/or hexamethylmelamine when two or more agents were selected. Specifically, 80% of the patients with advanced disease (Stage III or IV) received combination therapy (98% cyclophosphamide-based, 89% cisplatin-based, 31% doxorubicin-based, and 16% hexamethylmelamine-based), compared with single alkylating agents in the remaining 20%. Only 17% of these patients received 10 or fewer cycles of cytotoxic therapy, whereas 29% received more than 12 cycles. In addition, the intraperitoneal administration of colloidal isotopes was used in eight cases, whole pelvic irradiation in two, and a combination of the two in two.

After completion of the prescribed course of postoperative primary management and clinical assessment (extensive imaging not routinely used) failed to document persistent disease, a second-look procedure was performed. The median time interval between the initial definitive staging operation and the second-look laparotomy was 406 days, with 10% of the reexplorations occurring before 365 days and 10% after 630 days. A systematic exploration at the second-look operation was performed, including cytologic evaluation of peritoneal fluid or washings collected at the time of entry into the abdominal cavity. All visible or palpable areas suspicious for neoplasm were sampled, preferably by excision biopsy, and the specimens were forwarded for immediate histologic interpretation (frozen section). In the absence of documentable disease, specimens for microscopic review were obtained from the following sites: undersurface of hemidiaphragms, colic gutters, pelvic sidewalls, cul-de-sac, bladder, sigmoid, residual omentum, and retroperitoneal lymph nodes. In addition to preliminary frozen-section analysis, permanent-section results were reported within 24 hours. Hysterectomy and omentectomy were performed if omitted at the original staging/debulking procedure. Assessment of extent of disease in terms of size or volume (or both) was ascertained initially and again before closure. Adjunctive therapy after a positive second-look exploration was likewise individualized and included single-agent or multiagent chemotherapy, intraperitoneal isotopes, and pelvic or whole abdominal external radiation and, on occasion, combinations of these.

No operative mortality (60 days) was associated with any of the procedures. Fifteen patients (11.1%) experienced perioperative morbidity (Table I). All described conditions responded to conservative management, in-

Table V. Relationship of disease status at second-look laparotomy to extent of original tumor reduction in 118 cases

Original percent debulked	*No. of patients*†	*Negative reexplorations**	
		No.	*%*
100	45	37	82
95-99	27	14	52
90-94	18	6	33
<90	28	11	39
Total	118	68	58

*Absence of macroscopic or microscopic disease.

†Percent reduction in 17 cases was not estimable.

cluding transvenous radioscopic retrieval of a sheared central line.

Survival was measured from the date of the second-look operation, with follow-up times ranging from 15 months to 6 years. To analyze the variable follow-up times and censored survival data, the Kaplan-Meier method was utilized to estimate group survival. Tests of significance were based on two-sided log-rank tests for two-sample comparisons.

Results

The mean age of the 135 patients undergoing second-look laparotomy was 53.7 years. The distribution of age by decades showed a peak frequency during the fifth, sixth, and seventh decades; the youngest patient was 21 years of age and the oldest was 83 years.

Second-look results according to original surgical/pathologic parameters. Pathologic confirmation of active disease at the second-look procedure was obtained in 58 patients (43%). Stage III and IV lesions were documented at initial exploration in 77 of the 135 patients (57%) who eventually underwent reexploration (Table II). As anticipated, a significant number of patients with advanced disease who were treated at our institution showed progression of disease before completion of the prescribed adjuvant therapy and, therefore, did not require a second-look procedure. In addition, patients originally harboring Stage I disease occasionally elected to forego the second-look procedure, generally because of a lack of evidence substantiating procedural benefits. Therefore, the number of procedures performed in patients with Stage II disease, relative to patients with Stage I and Stages III and IV, appears to be disproportionately high as a result of these biases. Nevertheless, the percentage of patients having negative second-look procedures (no histologically demonstrable neoplasm) progressively decreased from 86% for Stage I to 38% for advanced disease (Table II).

As anticipated, serous lesions were the most frequent histologic cell type observed at primary operation in the second-look candidates, representing 58.5% of the total group. Patients originally harboring serous cystadenocarcinoma appeared to have a lower negative reexploration rate than did patients with the less common mucinous, endometrioid, or clear cell types (Table III). However, these differences were not statistically significant. The presence or absence of disease at the second-look procedure likewise was assessed as a function of the original histologic grade (Table IV), with no significant trends appreciated.

The patients presenting for second-look procedures were stratified according to the extent of the original tumor reduction (Table V). While the percentage of neoplasm initially removed could not be adequately determined in 17 patients, 45 (33.3%) of the 118 patients had been rendered free of macroscopic disease at initial laparotomy. Of the latter subgroup, 37 (82%) were free of disease at reexploration. The percentage of patients declared to be histologically free of disease at the second-look procedure declined abruptly if residual disease was present at the completion of primary surgical treatment.

Survival after second-look procedure according to surgical/pathologic parameters at reexploration. Survival of patients after the second-look procedure was assessed according to size of persistent tumor (Fig. 1). The 3-year and 5-year survival rates for patients without documentable disease were 94% and 83%, respectively. Minimal residual disease (<1 cm) was associated with a significant attrition relative to patients free of disease ($p < 0.001$), but no appreciable difference in survival was noted between patients with microscopic disease (43% at 5 years) and those with macroscopic disease <1 cm (39%). The poor prognosis for patients with tumor masses >1 cm is readily apparent and significantly less favorable than for patients with disease <1 cm ($p < 0.02$).

The presence of neoplastic cells in the peritoneal fluid or washings at the time of the second-look procedure was highly correlated with the extent of persistent disease and hence had prognostic value regarding postoperative survival. Of patients who had all random biopsies interpreted as negative, one had results of peritoneal cytologic study consistent with persistent disease. While cytologic samples were not available for assessment in 20 patients, the samples were positive in 52% of patients who had either microscopic disease or macroscopic disease <1 cm and 79% in patients who had lesions ≥1 cm. Survival after the second-look procedure was highly predictable ($p < 0.001$) on the basis of cytologic findings at reexploration (Fig. 2).

While sufficient tissue was occasionally not available for histologic grading in patients with microscopic per-

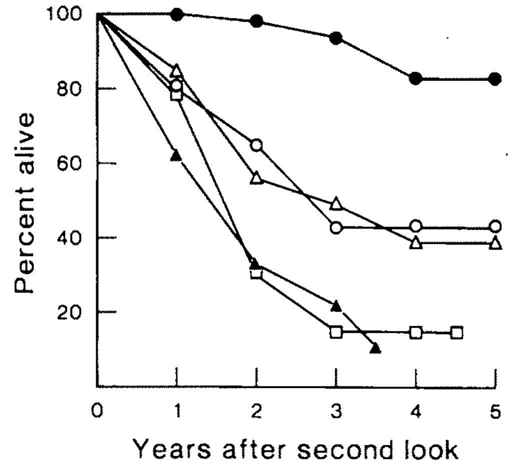

Fig. 1. Survival from second-look laparotomy to death from disease, according to tumor size at time of reexploration. ●——● = None; ○——○ = microscopic; △——△ = 0 to 1 cm; □——□ = 1 to 2 cm; ▲——▲ = >2 cm.

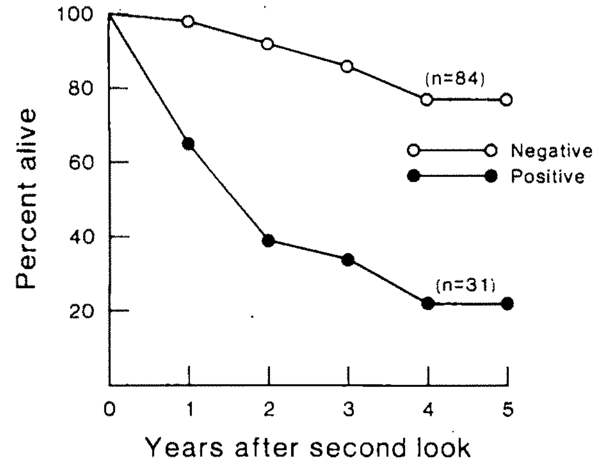

Fig. 2. Survival from second-look laparotomy to death from disease, according to peritoneal cytology.

sistence, progressive attrition in survival was related to increasing tissue dedifferentiation (Fig. 3). Longevity for patients with Broders' grade 1 neoplasms was similar to that for patients who had a complete histologic response and was significantly ($p < 0.02$) better than that of patients with higher grade lesions. The association between grade at second-look operation and survival was consistent at all levels, although no other intergrade differences were significant (grades 2 and 3 versus grade 4, $p < 0.09$).

The influence of residual disease after the second-look procedure on subsequent survival was evaluated (Fig. 4). When feasible, aggressive efforts were made to optimally reduce tumor volume at reexploration. Twenty-four patients either had only microscopic involvement or were rendered free of macroscopic disease at the second-look procedure, while an additional

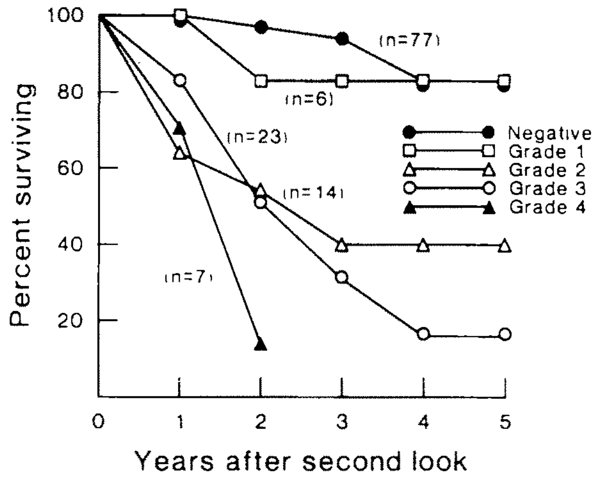

Fig. 3. Survival from second-look laparotomy to death from disease, according to histologic grade of tumor at reexploration. There was insufficient tissue in eight patients.

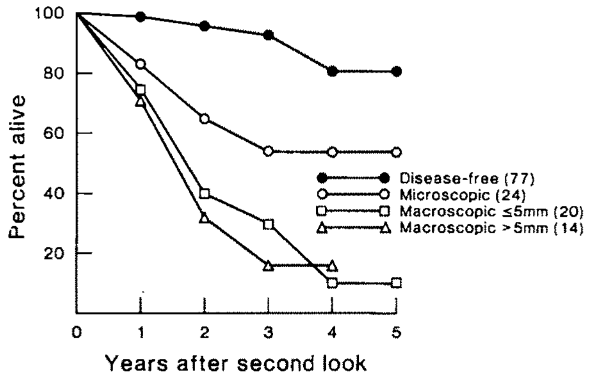

Fig. 4. Survival from second-look laparotomy to death from disease, according to residual tumor size at completion of reexploration.

34 patients had either visible or palpable residual tumor. The latter group was subdivided into those with lesions reduced to ≤5 mm and those with lesions >5 mm. Survival rates at 3 years were 93% for disease-free patients, 54% for patients with microscopic residual disease, 30% for patients with macroscopic disease up to 5 mm, and 16% for patients with macroscopic residual disease >5 mm. Although the extended prognosis for survival of the two subsets with gross residual disease was similarly poor ($p = 0.53$), the apparent differences between disease-free patients and those with microscopic residual disease, as well as between those with microscopic disease and those with macroscopic disease, were highly significant ($p < 0.001$ and $p < 0.02$, respectively).

The times and sites of subsequent failure were analyzed in the 77 cases in which there was no disease at reexploration. Recurrences have been detected in 12 patients (15.6%) between 6 and 41 months after operation; five patients had recurrence within 1 year of the second-look procedure and four had recurrence prior to the second year. Only one patient had treatment failure in the absence of either intra-abdominal or retroperitoneal disease. Four patients with recurrent disease after negative reexploration were among the 47 patients in whom the original cancer was confined to the pelvis, while eight patients were in the subgroup of 30 patients who were originally diagnosed as having advanced disease.

Comment

This series of patients with ovarian carcinoma constituted a rather homogeneous group, with the observation interval from 1977 deliberately chosen to coincide with the incorporation of cisplatin in the postoperative adjuvant treatment regimens. Among women clinically free of disease who underwent reexploration, a negative second-look laparotomy was correlated with the original stage of disease and the thoroughness of primary tumor reduction, in accordance with several previous reports.[3-6] Both parameters are indirect indices of the tumor cell burden at commencement of postoperative adjunctive therapy, and this finding illustrates the necessity for maximal tumor reduction at primary operation. The negative reexploration rate of 38% in patients originally presenting with Stage III and IV disease further emphasizes the inaccuracies of clinical assessment and the justification for continued utilization of invasive procedures for evaluating active disease. However, the categorical acceptance of second-look operations will require periodic reassessment and considerable moderation if enhanced salvage rates after positive second-look laparotomy are not forthcoming. In contrast, only one of seven patients originally designated as having Stage I disease had persistent disease at second-look operation, observations identical to those of Roberts et al.[6] Despite the low morbidity associated with second-look laparotomy, the low positive yield (14%) and the subsequent fractional salvage of this small subgroup warrant discontinuation of the practice of reexploration in the entire Stage I population. Rather, a concerted effort must be made to identify select subsets of this population who are at substantial risk for persistent or recurrent disease and who would benefit from a second operative procedure.

The percentage reduction of tumor volume at primary operation predicted with reasonable success the disease status at the second-look procedure—consistent with previous reports correlating cytoreductive surgical procedures and enhanced survival.[7-11] Negative reexploration rates of 82%, 52%, and 37% were associated with complete, $\geq$95%, and <95% tumor reduction, respectively. These results again stress the merits of maximal reduction, as evidenced by the precipitous decline in disease-free status at the second-look operation in patients with only minimal macroscopic disease originally. Further fractionation of the group that had <95% debulking failed to delineate more favorable subgroups, presumably a reflection of the concerted efforts at primary operation toward the optimal reduction in all patients or the influence of a critical tumor volume on tumor biology (or both). However, caution must be exercised in interpreting these results since patients with Stage I and II disease, by definition, would constitute a significant number of these two more favorable groups and, hence, may simply mirror their more limited primary disease rather than the degree of original tumor reduction.

Prognosis after a second-look laparotomy was unfavorably influenced by increasing occult tumor size at reexploration, increasing histologic grade of the residual carcinoma, presence of exfoliated neoplastic cells in peritoneal fluid, and residual tumor at completion of the second-look operation. Schwartz and Smith[3] reported 5-year survival rates after second-look procedures of 72% and 38% in patients with no evidence of disease and microscopic disease, respectively. Our equivalent subgroups paralleled their findings, with survival rates of 83% and 43%, respectively. However, unexpectedly, patients with macroscopic disease of <1 cm at reexploration fared as well as patients with only microscopic persistence and did substantially better than those patients with lesions exceeding 1 cm. Potentially, the more favorable survival in this group reflected the value of secondary cytoreductive surgical procedures. This supposition was indirectly addressed by assessing survival after reexploration as a function of residual tumor size at the completion of the second-look procedure. The initial attrition rates and subsequent longevities were similar for patients with macroscopic disease, irrespective of residual tumor size. Demonstrable benefit from additional debulking could be ascribed only to patients (nine of 43) rendered free of macroscopic disease through such efforts. Nevertheless, we agree with other reports[12, 13] suggesting minimal value in further aggressive tumor reduction, unless complete removal of all macroscopic disease can be attained. These results attest to the absolute necessity for developing effective salvage therapy before enhanced survival in patients with persistent disease at second-look laparotomy can be achieved.

The importance of the original grade as related to second-look findings has not been consistent[3, 5, 6, 14] and was of no apparent significance when applied to this population as a whole. However, the increasing grade of persistent neoplasm at the second-look procedure was associated with decreasing long-term survival. Tissue heterogeneity may be less common under these more uniform conditions, thereby leaning toward such stratification. Of particular interest was the survival associated with patients having grade 1 lesions, which did not differ from the survival of patients who were free of disease. Recently, Copeland et al.[15] have reported similar observations and have addressed appropriate approaches regarding subsequent therapy.

As obtained at laparotomy, cytologic assessment of peritoneal fluid or washings used as a single parameter was an extremely sensitive predictor of survival, confirming similar observations by Stuart et al.[16] While our patient population with negative cytologic findings included 18 (six microscopic, eight <1 cm, four >1 cm) with histologically documented disease, the overall 3- and 5-year survival rates for this group differed only minimally from those of patients who were histologically free of disease. The explanation for these favorable survival rates is not readily apparent. However, Copeland et al.[15] have discussed several biologic characteristics that might contribute to favorable survival despite persistent disease at subsequent laparotomies. Possibly an inherent trait of one or more of these described states may be the loss of cellular exfoliation.

At least in part, the recurrences subsequently encountered within 12 to 24 months in patients after negative second-look operations are a measure of procedural limitations. The recurrence rates for patients with Stages I and II collectively and advanced disease were 8.5% and 27%, respectively, with nine of 12 failures being detected within 24 months of reexploration. In addition, only a single failure site was not theoretically accessible to surgical and histologic analysis at the second-look operation. The limitations of the procedure are readily apparent, but, at present, diagnostic alternatives are not available. While ovarian tumor markers will undoubtedly replace these practices in the future, their applicability at present remains investigational. The value of continued or altered therapy after negative second-look laparotomy, as inferred by the results of Raju et al.,[13] may warrant further clinical evaluation in patients who had advanced disease originally.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. ALLAN J. JACOBS, St. Louis, Missouri. Surgical restaging in patients who are in complete remission following definitive primary treatment for ovarian carcinoma has assumed an increasingly prominent place in the gynecologic literature. This article will help us in our attempt to determine the appropriate role of this operation. It reports a large volume of carefully documented work by excellent physicians. In discussing the importance of this work, I will compare Dr. Podratz's data with those reported in two other recent articles from Mount Sinai[1] and the University of California (Los Angeles).[2]

The number of patients undergoing second look after treatment for extrapelvic disease is comparable among these three series, ranging from 56 at UCLA to 83 at Mount Sinai. In all three series, the initial operation was followed by a course of chemotherapy. Shortly after completion of chemotherapy, a second operation was performed upon consenting patients in complete clinical remission. The operation, which was comparable in the three series, consisted of an exhaustive exploration, with multiple biopsies, both of the peritoneal cavity and of the retroperitoneum. The indications for and frequency of repeated cytoreduction in patients with persistent tumor found at second look were not explicitly treated in any of the three papers.

The findings at operation in all three series were quite similar. Thirty-two percent to 41% of patients originally presenting with extrapelvic disease (Stages III and IV) had no histologic or cytologic evidence of residual tumor at second look operation. The overwhelming majority of these patients remained in remission and are still alive. An additional 11% to 15% had microscopic disease. Approximately half of this group survived for at least 3 years, at all three institutions. Even among patients with gross residual disease remaining at the time of second look, a significant number of patients enjoyed prolonged survival. The likelihood for a good clinical result in these patients was directly related to thorough debulking at the time of second look. Podratz' data suggest that the authors recognized this, since more than half of their patients had tumor masses >1 cm at second look had them reduced to less than this during the second-look operation.

It would have been interesting if the authors had analyzed their findings as a function of the specific adjuvant treatment regimen given after the first operation. I believe that the second-look operation is an integral part of a total treatment regimen. Findings at second look are influenced by the type of treatment the patient has previously received. For example, data from UCLA indicate that the proportion of negative second-look operations in patients in complete clinical response is lower in patients treated with an alkylating agent alone than in those who received combination chemotherapy. Therefore, one must assume, unless it is otherwise demonstrated by empirical data, that the findings will differ according to the antecedent treatment. Indeed, it may be that indications for, and timing of, such operations ought to vary with the primary treatment of that disease.

I would like to ask a few questions. What was the relationship between chemotherapy regimen and second-look findings? What sort of salvage therapy was used in patients with positive findings at second-look operation to achieve the substantial survival reported? Have the authors had any experience with the CA-125 antigen,[3] and will this affect the necessity for, or timing of, second-look operation?

In this excellent report, as well as in other work, the authors have added greatly to our understanding of how to manage ovarian carcinoma. I believe that the following conclusions can be drawn from their work. Comprehensive surgical restaging can be performed with minimal morbidity. If no tumor is found following such an operation (and I emphasize that all of the many biopsies they do are necessary, in view of the frequent prevalence of microscopic residual disease), chemotherapy may reasonably be discontinued. If not, the ability to detect minimal residual disease, and to attack it with further surgical debulking and postoperative adjuvant therapy, probably enhances the duration of survival and chance of cure. Thus, if feasible, secondary cytoreduction should be performed at this time. The value of second-look surgical procedures can be rigorously determined only by randomized trials, which are probably not forthcoming. However, comprehensive secondary restaging should, in my opinion, no longer be considered investigational. It should be a part of the treatment plan of every physician treating ovarian carcinoma. It should be used in all fit patients in complete remission after primary therapy for tumors beyond Stage I and in selected patients with Stage I tumors as well.

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Dr. Arthur L. Herbst, Chicago, Illinois. Dr. Podratz and his colleagues have provided us with a comprehensive review of 135 patients with ovarian carcinoma who underwent second-look laparotomy after 1 year of therapy. The series is meticulously documented and carefully analyzed. A number of parameters were evaluated to ascertain the factors which appeared to affect patient survival. Not surprisingly, those with high-stage disease at initial operation did worse than those with low-stage disease. Effective initial tumor debulking was also associated with a favorable prognosis. However, somewhat surprisingly, the original histologic grade and tumor subtype did not appear to affect the findings at second-look operation. In this series, 38% of patients who initially presented with Stage III or IV ovarian carcinoma had a negative second-look procedure. These findings are similar to others reported in the literature, such as the 56 Stage III cases recently reported by Berek et al.[1]; 32% of these patients were free of the disease at second-look procedure. However, in Berek's series, as well as in some others reported in the literature, favorable prognosis was also associated with low tumor grade at initial operation. In the current series, survival after second-look procedure was correlated to the presence or absence of residual tumor as well as to the size of the residual disease found at second-look operation. However, patient survival after second-look operation was related to histologic grade, in contrast to the results at initial operation. What might be the explanation of the correlation of patient survival with tumor grade at second-look operation but the lack of such a correlation with tumor grade at initial operation? One can only speculate, and I suspect that the results suggest that the initial response to chemotherapy may not necessarily be determined by the grade of the carcinoma. However, those cells that are resistant to chemotherapy are the ones that will be present at the time of second-look operation. We do not have currently available a very effective second-line program for treating individuals who have failure of first-line therapy. Thus I suspect the difference in survival related to tumor grade after second-look reflects the "natural history" of the growth of these chemotherapy-resistant cells in the patient. This led to a 3-year survival of 83% in those with grade 1 tumors in comparison to 31% of those with grade 3 and only 14% for those with grade 4 tumors. It is of interest that those with grade 1 tumors had a 3-year survival after second-look operation which was as good as that of those who had a negative second-look procedure.

There are a few areas for which I would appreciate Dr. Podratz' comments. The manuscript states that the authors chose patients treated in 1977 as a time to initiate their analysis, since that is when platinum-containing combination regimens began to be used. The analysis presented in the manuscript combines those receiving platinum-containing combinations and those receiving single-agent alkylating therapy. It would be helpful to compare these results with those of other series if the patients with platinum treatment were presented separately. Can Dr. Podratz provide us with any indication of the results of those who received initially only multiple-agent platinum-containing chemotherapy? In addition, the manuscript states 87% of the patients were treated with some sort of chemotherapy. Eight other patients received colloidal isotope treatment, two others underwent whole abdominal radiation, and two received a combination of whole abdominal radiation and colloidal isotope treatment. These 12 form 9% of the series and there were 87% who received chemotherapy. I wonder what treatment was given to the remaining 4%? Finally, 10 of the patients were under the age of 29 at the time of initial diagnosis and one of them was reported to be 21 years of age. I wonder if any of these patients had a borderline ovarian carcinoma?

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Dr. Eduard Eichner, Cleveland, Ohio. My experience has not been as extensive as that of the authors, but I have had a couple of things that have upset me a little bit. In the early group of second-look procedures, my patients simply "went to pot" immediately afterward, as if all immunity had disappeared.

This problem has not been presented by the authors, and I wonder what their experience in that line has been.

Dr. Kenneth W. Crabb, St. Paul, Minnesota. Unfortunately, a few patients with a negative second-look procedure develop recurrent disease at a later time. What are your thoughts and ideas about additional studies that could be done on these patients with a negative second-look procedure to decrease the incidence of later recurrence?

Second, in patients with microscopic residual disease at the time of the second-look procedure, would you advocate a third look after additional therapy?

Dr. James G. Blythe, St. Louis, Missouri. What is your second-line treatment now for those patients who have a positive second-look procedure, and are you giving any thought to using full pelvic and abdominal radiation on those patients resistant to platinum?

Dr. Podratz (Closing). We wish to express our appreciation to Drs. Jacobs and Herbst for their formal critiques. Our manuscript addressed the influence of various surgical/pathologic variables at primary operation and at reexploration on observations at second-look laparotomy and on survival after reexploration, respectively. While survival analyses have been conducted as a function of individual cytotoxic agents, various agent-based regimens, and different modes of salvage therapy, discussion of these data is beyond the scope of this presentation. However, from an informational standpoint, salvage therapy during the initial phases of the study generally consisted of second-line cytotoxic agents and occasional intraperitoneal isotopes. During the latter phases, salvage therapy was dependent on the extent of tumor size at completion of the second-look procedure. Patients harboring residual lesions <5 mm in diameter received whole abdominal irradiation (3000 rad, with shielding of liver and kidneys at 2250 and 2000 rad, respectively), with additional boosts of 4250 rad to the periaortic and diaphragmatic areas and of 5100 rad to the pelvis. When lesions exceeding 5 mm were present, systemic chemotherapy was used, with more recent incorporation of intraperitoneal cytotoxic chemotherapy.

In response to Dr. Herbst's concern regarding borderline neoplasms and the 4% not accounted for in the treatment analysis, no patients with borderline lesions were included and approximately 4% of the population was not treated. Patients with favorable Stage I lesions were randomized to receive L-phenylalanine versus no postoperative adjunctive therapy, with the latter accounting for nontreated patients undergoing second-look procedures.

Dr. Eichner's observation of occasional rapid deterioration after second-look operation was likewise noted at our institution; approximately one third of the patients who had positive peritoneal cytologic tests or residual disease exceeding 5 mm died of disease within 12 months. We suspect the relationship to operation is coincidental and presumably correlates to the development of pleiotropic drug resistance and progressive tumor growth.

While we continue to routinely perform second-look and third-look operations when indicated, the categorical acceptance of these procedures in the overall treatment schema of ovarian cancer must be cautious. The reported recurrence rates of as much as 50% after negative second-look procedures, together with very limited salvage therapy, rival the potential benefits that patients might derive from reexplorations. The use of tumor markers such as CA-125 (described by Drs. Bast and Knapp from Boston) probably will reduce the required number of invasive procedures. However, until adequate clinical trials, particularly in patients with minimal residual disease, have been forwarded and confirmed, we caution the premature acceptance of this immunoassay.

Maternal weight and pregnancy complications

John A. Garbaciak, Jr., M.D., Michael Richter, M.D., Steve Miller, M.S., and John J. Barton, M.D.
Chicago, Illinois

The effect of obesity alone was investigated among 16,858 women who were delivered of their infants within a 12-month period. Complete analysis was possible for 9667 patients who were divided into four weight categories and separated into two groups, with and without complications. Perinatal mortality, infant size, and the primary cesarean delivery rate were calculated for each group. Among 2597 women with antenatal complications, there was a significant increase in perinatal mortality ($p < 0.001$), primary cesarean delivery ($p < 0.02$), and mean infant birth weight ($p < 0.01$) in the obese and the morbidly obese gravid women. Among 7070 women without antenatal complications there was a significant increase in primary cesarean delivery ($p < 0.001$) and mean infant birth weight ($p < 0.01$) but not perinatal mortality in the obese and the morbidly obese gravid women. Obesity alone does not appear to affect the perinatal mortality rate but it increases the likelihood of cesarean delivery in the morbidly obese patient. (AM J OBSTET GYNECOL 1985;152:238-45.)

Key words: Obesity, complications, cesarean section

Obstetricians have always felt that maternal obesity means an increased risk of pregnancy complications. Over the past 30 years, numerous authors have cited retrospective and prospective studies, with and without controls, that attest to an increased incidence of hypertension, preeclampsia, gestational diabetes, malpresentation, and postpartum hemorrhage in the obese gravid women.[1-6] Discussions related to significant differences in incidence of cesarean delivery, infant size, and perinatal mortality rate have received recent attention in the literature.[7-9]

The previous studies compared obese patients with groups of nonobese patients. These two groups included patients who had other factors complicating pregnancy. Because additional factors such as hypertension, diabetes, preeclampsia, prematurity, intrauterine growth retardation (IUGR), infection, etc., were not evenly distributed between the two groups, conclusions regarding the effect of obesity alone upon perinatal mortality, infant size, and primary cesarean delivery rate cannot be accurately drawn.

It is the purpose of this analysis to determine the effect of obesity per se, when no other antenatal complications are present, on perinatal mortality, infant size, and primary cesarean delivery rate.

Material and methods

The analysis of 16,858 records of women delivered between January 1, 1982, and December 31, 1982, was performed with computer assistance from the University of Illinois Center for Health Services Research. Maternal and infant data were abstracted from the maternity and newborn records onto a uniform hard-copy abstract for data entry into a central computer. Deliveries occurring at 18 institutions within the University of Illinois perinatal network made up all of the 16,858 cases. Abstraction was performed by experienced personnel, familiar with obstetric data and obstetric records, for the sole purpose of obtaining accurate data.

A complete description of the perinatal data gathering system has previously been published.[10] Of the 16,858 cases, sufficient data were present to include 9667 patients. The data used were obtained from the

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Table I. Weight categories and antepartum complications

	Weight category				
	Undernourished (<85% of ideal body weight)	*Normal weight (85% - 120% of ideal body weight)*	*Obese (120% - 150% of ideal body weight)*	*Morbidly obese (>150% of ideal body weight)*	*Total*
No antepartum complications	435	5407	969	259	7070
Antepartum complications	172	1763	476	186	2597
Total	607	7170	1445	444	9667

Table II. Antepartum complications and their frequencies

	Weight category								
	Undernourished		*Normal*		*Obese*		*Morbidly obese*		
Antepartum complication	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*p*
Hypertensive disease	6	0.9	141	1.9	101	7.0	76	17.2	<0.05
Preeclampsia-eclampsia	23	3.8	317	4.4	95	6.6	30	6.9	<0.05
Diabetes	7	1.2	102	1.4	56	3.9	46	10.4	<0.05
Heart disease	15	2.5	140	1.9	31	2.1	11	2.5	NS
Vaginal bleeding	36	5.9	479	6.7	93	6.4	36	8.2	NS
Anemia	33	5.4	311	4.3	46	3.2	10	2.4	<0.05
Thyroid disease	4	0.7	80	1.1	23	1.6	8	1.8	<0.05
Renal disease	3	0.5	34	0.5	6	0.4	2	0.4	NS
Syphilis	2	0.3	32	0.4	8	0.5	4	1.0	<0.05
Incompetent cervix	2	0.3	27	0.3	6	0.4	2	0.4	NS
Thrombophlebitis	2	0.3	8	0.1	6	0.4	2	0.4	<0.05
Urinary tract infections	36	5.9	419	5.8	116	8.0	42	9.4	<0.05
Systemic lupus erythematosus	0	0.0	6	0.1	1	0.1	1	0.2	NS
Isoimmunization	3	0.5	42	0.6	8	0.5	5	1.2	NS

χ^2 analysis was used to determine p values.

University of Illinois and its affiliated perinatal network members.

Obesity in pregnancy has received numerous definitions. Body weight >20% above the normal weight for height is often used, as well as a description of the fat thickness with calipers used to measure various skin folds. Some authors[5] use actual body weight >80 kg (175 pounds) during pregnancy while others use a body weight based on height varying between 50% and 300% above the ideal prepregnant weight for height.[6] The most frequently used definition for morbid obesity during pregnancy is a maternal weight >90 kg (200 pounds).[8] This definition ignores height and does not differentiate between prepregnant weight and possible massive antepartum weight gain.

Normal weight was determined by using the Metropolitan Life Insurance Company tables based on height. For this reason, it was necessary to have the patient's height and prepregnant weight recorded. Either one or both of these parameters were missing in 7191 records. The remaining 9667 patients were then classified into one of four categories based on their nonpregnant weight. Each of these categories was divided by separating those patients with antenatal complications from those with no evidence of complications. The categories, their subdivisions, and numbers of patients in each are listed in Table I. The list of antepartum complications and their frequencies in different weight categories is noted in Table II.

The hypothesis that no significant difference in perinatal mortality and primary cesarean delivery rate existed among undernourished, normal, obese, and morbidly obese patients, with and without antenatal complications, was tested with the χ^2 analysis. The hypothesis that no significant difference in infant weight existed among these four groups was tested by means of a one-way analysis of variance. The correlation between infant birth weight and maternal weight was estiamted by using the omega squared coefficient for measurement of association. The neonatal weight difference between normal patients and those with antepartum complications within each category was tested

Table III. Perinatal mortality

	Weight category								
	Undernourished		*Normal weight*		*Obese*		*Morbidly obese*		
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*p*
Antepartum complications	172/607	28.3	1763/7170	24.6	476/1445	32.9	186/445	41.8	<<0.001
Perinatal mortality (No./1000)	7/607	11.5	48/7170	6.7	24/1445	16.6	10/445	22.5	<0.001
Perinatal mortality with antepartum complications (No./1000)	3/172	17.4	21/1763	11.9	15/476	31.5	7/186	37.6	<0.01
Perinatal mortality without antepartum complications (No./1000)	4/435	9.2	27/5374	5.0	9/969	9.3	3/259	11.6	NS

Table IV. Primary cesarean section

	Weight category								
	Undernourished		*Normal weight*		*Obese*		*Morbidly obese*		
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*p (between)*
Primary cesarean section with antepartum complications	24/156	15.4	294/1638	17.9	101/424	23.8	33/146	22.6	<0.02
Primary cesarean section without antepartum complications	42/415	10.1	526/5065	10.4	105/850	12.4	43/219	19.6	<0.001
p (within)	NS		<0.001		<0.001		NS		

with the Student t test for independent groups with homogeneous variances.

Results

Antenatal complications. Table II shows that obese and morbidly obese individuals are at significantly high risk for having hypertensive disease, preeclampsia, diabetes mellitus, and urinary tract infections. Although a statistically significant difference between weight categories was noted for patients with thyroid disease, syphilis, and thrombophlebitis, the small numbers in each cell must give caution to their true significance. A significantly lower incidence of anemia was noted in the obese and morbidly obese individuals. This corresponds to a higher incidence of anemia in those patients categorized as undernourished.

Intrapartum complications

Maternal. Our data base allowed us to look at the frequency of placenta previa, abruptio placentae, cord prolapse, premature labor, and those patients with more than one of the above complications. A significant increase in premature labor and patients having more than one of the above complications was noted in undernourished individuals only.

Fetal. Cord accidents were noted in 6.7% of morbidly obese patients without antenatal complications and only 4.0% of the normal-weight patients. Shoulder dystocia occurred approximately twice as often in the morbidly obese patient without antenatal complications (1.78%) when compared to the normal-weight patient (0.81%). Meconium was noted in 23.5% of the obese patients without antenatal complications, a figure which differed significantly from the 15% of undernourished patients and the 18% of normal-weight patients. Late decelerations were noticed with significantly increased frequency (7.55%) in the morbidly obese patient without antenatal complications compared to 3.83% of the normal-weight patients. Fetal acidosis documented by scalp pH or cord blood pH was not significantly different between weight categories.

Perinatal mortality. Table III shows that there is a significant increase in perinatal mortality as a function of maternal weight ($p < 0.001$). The incidence of antepartum complications also increased as a function of maternal weight ($p < < 0.001$). In those patients without antepartum complications, there was no significant difference in perinatal mortality regardless of weight. In those patients with antenatal complications there was a significant difference ($p < 0.01$) in perinatal mortality as a function of maternal weight. Therefore, it appears that maternal weight itself does not significantly affect perinatal mortality. However, differences in maternal weight plus the presence of antepartum complications appear to significantly increase perinatal mortality.

Cesarean delivery. The primary cesarean rate was calculated from the total number of patients delivered

Table V. Birth weights

	Weight category				
	Undernourished	*Normal weight*	*Obese*	*Morbidly obese*	*p (between)*
Mean infant weight (gm) without antepartum complications	3150 ± 552	3351 ± 545	3486 ± 576	3612 ± 550	<0.01
Mean infant weight (gm) with antepartum complications	2968 ± 652	3197 ± 637	3309 ± 694	3452 ± 694	<0.01
p (within)	<0.01	<0.01	<0.01	<0.01	

minus those patients undergoing a repeat cesarean section. Table IV reveals that among women with antepartum complications, there was a significant increase ($p < 0.02$) in primary cesarean deliveries. Among women without antenatal complications, there was also a significant increase ($p < 0.001$) in primary cesarean deliveries especially apparent among the morbidly obese patients. Within each weight category, cesarean rates in those patients with antenatal complications are significantly higher ($p < 0.001$) than rates in those patients without antenatal complications only in the normal and obese categories.

Infant birth weight. Analysis of birth weights is shown in Table V. In patients without antenatal complications, a significant increase ($p < 0.01$) in infant weight is noted as maternal weight increases. In patients with antenatal complications, this significant increase ($p < 0.01$) in infant weight is likewise noted although the mean weights were decreased in each category. This decrease was statistically significant ($p < 0.01$) within each category. An estimate of the strength of relationship between maternal weight and fetal weight was obtained by the omega squared coefficient for measurement of association. This test revealed that only 24% and 27% of the increase in fetal weight in women with and without antenatal complications, respectively, could be attributed to maternal weight alone.

Comment

Numerous studies have repeatedly shown that the obese gravid woman is more prone to antenatal and intrapartum complications. Analysis of data for the obese patients in previous studies included those with antenatal complications together with patients who did not have antenatal problems. Our study defined a group of women where maternal weight was the only variable present among pregnant women with no other antenatal complications. We also looked at differences between women defined as obese and those defined as morbidly obese. This enabled us to look clearly only at maternal weight as it affects intrapartum maternal and fetal complications, perinatal mortality, incidence of primary cesarean delivery, and infant birth weight.

This analysis gives evidence for the association of maternal obesity with a significant increase in antenatal complications and an increased incidence in perinatal mortality. However, if we look at those patients without antenatal complications, it can be seen that no significant difference in perinatal mortality was present between any of the four weight categories. It would appear that maternal weight, in and of itself, when no other antenatal complications are present, is not associated with a poorer pregnancy outcome. However, when we looked at intrapartum maternal and fetal complications, it was interesting to note the increase in shoulder dystocia and cord accidents in obese and morbidly obese patients without antenatal complications. There was also a significant increase in meconium staining and late decelerations of the fetal heart rate noted in the morbidly obese patients without antenatal complications. These observations may have had an effect on the increased incidence of primary cesarean delivery in the morbidly obese patient without antenatal complications.

In 1962 the British[3, 4] reported that obese patients had an increased incidence of cesarean deliveries. Subsequent reports[6, 8] agreed with investigators who reported in 1945[1] and 1956[2] that there was no significant increase in cesarean deliveries in obese gravid women. Our data suggest that a significant increase in cesarean deliveries is present as a function of maternal obesity. If obese gravid women are at increased risk for antenatal complications, this increase in primary cesarean deliveries could be expected. However, between each weight category in those patients without antenatal complications, a significant increase in the number of cesarean sections was present for those patients who were morbidly obese. Since a significant increase in meconium staining, late decelerations, and cord accidents was noted in this group, these findings could contribute to a higher primary cesarean rate. Can this increase also be attributed to the significant increase in fetal size?

Previous reports have shown that fetal weight is directly proportional to maternal size.[6, 8, 11] Emerson[4] reported that more than 50% of overweight women had babies who weighed >8 pounds (3630 gm). Eastman and Jackson[11] have shown a straight-line correlation for weight of the newborn infant when maternal weight gain in pregnancy exceeded 10 pounds. They also showed a direct correlation between prepregnant maternal weight and eventual infant birth weight. They felt that these two factors acted independently and additively on the baby's weight and concluded that mothers who are heavier prior to conception will be delivered of heavier babies. Edwards et al.[6] also reported a significant increase in mean infant birth weight in obese women. Gross et al.[8] reported a significant increase in macrosomic babies in an obese population but also noted a significant lengthening of the gestational period.

Our data reveal a significant difference in mean infant birth weight among patients with as well as those without antenatal complications. As the weight of the mother increases, so does the weight of the newborn infant. This relationship is also apparent for those patients with antenatal complications. Analyzing the correlation of fetal weight with maternal weight revealed that only 24% and 27% of the increase in fetal weight in women with and without antenatal complications, respectively, could be attributed to maternal weight alone. This is not a significantly high proportion of the variance. This tendency for increased birth weight as maternal weight increased was also present in those women who had antenatal complications. The mean birth weight within each category was significantly lower than for those women without antenatal complications as would be expected. Even though antepartum complications significantly decrease birth weight in all weight categories, a larger prepregnant weight corresponded to a significantly increased fetal weight.

Gross et al.[8] have recently reported a higher incidence of macrosomic babies in their population of obese women. If this increase of macrosomia is present in our population, it could serve as an explanation for the increase in primary cesarean sections even though this was not found in Gross's study. This difference between studies may be due to the different way obesity was defined in his study and the fact that he did not differentiate obese women from morbidly obese women. Further refinement of our data base will allow us to see if a significantly larger proportion of obese and morbidly obese women are delivered of babies >4000 gm.

The reason or reasons for this increase in cesarean rate are not clear in those patients without antenatal complications. One may postulate increased fetal size, an increase in maternal pelvic soft tissue that could narrow the diameters of the birth canal, or the increase in intrapartum meconium staining, late decelerations, and cord accidents. Whatever the reasons, it should be noted that there no longer appears to be a hesitancy to perform an abdominal delivery in a morbidly obese patient as has been alluded to in a previous report.[7]

There is no denying that maternal weight has an effect on pregnancy. Undernourished patients are at risk for anemia and premature labor. Close attention to their diet and weight gain is necessary. Monitoring these patients with more frequent office visits and educating them to report subtle signs of premature labor should enable more of them to carry their pregnancies to term and improve perinatal survival.

The best way to prevent the problems associated with morbidly obese and obese gravid women would be to eliminate the prepregnant morbidly obese state. Since this is not realistically possible, it is necessary for those attending this type of patient to be aware of the specific complications that were noted in our population. We recommend that all obese and morbidly obese gravid women have a glucose screening test for diabetes at their initial prenatal visit and have it repeated at the beginning of the third trimester if the previous screening was normal. Since the obese and especially the morbidly obese patients are at increased risk for hypertensive complications, blood pressure monitoring should be carried out with the appropriate size of blood pressure cuff at 1-week intervals beginning after the second trimester. Any sustained elevation should be quickly and correctly managed with antihypertensives, bed rest, and/or hospitalization for frequent monitoring of both maternal and fetal status.

It is already recommended that all pregnant patients be screened for asymptomatic bacteriuria at their initial visit. We feel that the obese and morbidly obese patient should be screened for bacteriuria in subsequent trimesters since their risk for developing a urinary tract infection is more than 9%.

It seems prudent to avoid vaginal delivery in the morbidly obese patient who demonstrates any type of dystocia not easily correctable. This is especially true regarding the use of forceps. A further analysis of our data should allow us to see if an increased use of forceps occurred in those morbidly obese patients who developed shoulder dystocia. We will also look at 5-minute Apgar scores and the amount of blood loss and blood transfusions.

The effects of maternal weight on pregnancy outcome vary from population to population. Hypertension, diabetes, urinary tract infection, and anemia all occur with increased frequency and exert their effect on perinatal outcome. Obesity alone also seems to affect the intrapartum course and eventual mode of delivery. Maintaining awareness of the specific problems related to maternal weight and pregnancy should enable the practitioner to maximize efforts to reduce perinatal morbidity and mortality.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. MICHAEL W. VARNER, Iowa City, Iowa. A person whose excess weight has a negative impact on their health or function may be termed obese. There is no doubt that obesity is becoming a progressive health problem in this country. Although the exact incidence of the problem depends on the definition of obesity that is used, the incidence clearly increases with progressive age and decreases with extent of formal education. Obesity is more common in women than in men and its study is thus of particular importance to obstetrician-gynecologists.

The authors have defined obesity as >120% of ideal prepregnant weight for height, which is an acceptable definition. Their definition results in 19.55% of their studiable population being defined as either obese or morbidly obese, an incidence comparable to that of recent population studies of reproductive-aged women.

The authors have considered the problem of obesity and pregnancy from an angle that has not been addressed previously. By controlling for the presence or absence of antepartum complications, they have shown that progressive obesity is associated with an increased likelihood of perinatal mortality, higher mean infant birth weight, and need for abdominal delivery. Their data also show that progressive maternal obesity per se is associated with a progressive risk of antepartum complications when compared to their normal-weight group.

In conjunction with Drs. Kolberg, Johnson, and Railsback, I recently participated in a review of the experience at The University of Iowa Hospitals with obesity and pregnancy. Using a definition of weight >250 pounds during pregnancy, we found that, when compared to control subjects matched for age, parity, and year of delivery, obese gravid women have significantly greater risks of certain antepartum complications, including gestational diabetes, hypertension, and prolonged gestation.

While the article lists those problems considered as antepartum complications, it does not distribute their relative frequencies among the maternal weight groups. Could the authors comment on the relative distribution of antepartum complications between their normal-weight and obese groups?

The intrapartum time course of the obese pregnant woman is also a period of increased risk to mother and baby. We have found an increased incidence of oxytocin augmentation, prolonged second stage of labor, shoulder dystocia, and failed induction of labor in obese parturients. We have also seen an increased risk of primary cesarean section, for both fetopelvic disproportion and failure to progress in labor. We have not seen any increased incidence of fetal distress. While I realize that a discussion of specific intrapartum complications is beyond the stated purpose of this article, I am nonetheless curious whether the authors have any information on their patients' intrapartum outcomes?

I believe it is also important to return for a moment to the authors' stated topic, namely, maternal weight and pregnancy complications. While they address the problems of the obese gravid woman, they also provide us with important information on the undernourished pregnant woman. Their group of undernourished patients also had a higher incidence of antepartum complications than those women of normal weight. Although their undernourished group did not have higher average birth weights or rates of cesarean section, they did have higher perinatal mortality rates, with or without antepartum complications. I wonder, in addition, if the authors could comment on the relative distribution of antepartum and/or intrapartum complications between their undernourished and normal-weight groups?

In conclusion, the authors have shown us that extremes of maternal preconception weight do place a pregnancy at increased risk. I wonder if they can give us any recommendations for alteration of our routine antepartum and/or intrapartum care that might allow us to anticipate, and hopefully prevent or minimize, these associated complications?

DR. LILLIE-MAE PADILLA, Indianapolis, Indiana. Obesity is a significant health problem in industrialized nations. Unfortunately, we do not have a precise definition of obesity. In the nonpregnant population obesity is usually defined as body weight in excess of 20% above the ideal weight (actuarial tables); however, in the pregnant patient the weight range used to define the obese patient varies from >80 to 114 kg. It is well accepted that being grossly overweight is associated with higher maternal and fetal morbidity and mortality. Obese pregnant patients are consequently considered high-risk patients. Specifically the risk of developing hypertension, diabetes, toxemia, and thromboembolic disease in obese pregnant patients is much greater than in normal-weight gravid women. Furthermore obesity is associated with increased perinatal mortality.

In this retrospective study of 9667 patients, Garbaciak et al. have used prepregnant patient weights and heights to define obesity. The obese patients were subdivided into two groups: (1) patients with antepartum complications and (2) patients without antepartum complications. They studied the effects of obesity on perinatal mortality, infant size, and incidence of cesarean section.

The present study reports an increasing incidence of antepartum complications with increasing maternal weight. This has been an observation noted by several older as well as more recent studies. Odell and Mengert[1] reported toxemia of pregnancy in 31.4% of their obese patients. Petry[2] reported an increased incidence of toxemia, essential hypertension, and maternal death. Kerr[3] found an increase in preeclampsia and essential hypertension. Emerson[4] confirmed these findings but also noted an increased frequency of antepartum hemorrhage and fetal malpresentation in obese patients. Tracy and Miller[5] observed the increased incidence of toxemia and maternal death in obese patients. In addition, diabetes, pyelonephritis, and prolonged labor were also noted to be significantly increased. Hypertension and diabetes were also found to be increased in the obese patients by Roopnarinesingh.[6] Freedman et al.[7] reported the highest frequency of toxemia (66%) and abnormal presentation (19.9%) in their obese patients. Edwards et al.[8] found a significantly increased incidence of hypertensive disorders of pregnancy, gestational diabetes, inadequate weight gain, and wound-episiotomy infection. Gross et al.[9] found an increased risk for antepartum complications in the current pregnancy studied in obese patients in the form of chronic hypertension (7.2%), diabetes mellitus (gestational, 6.5%; insulin-dependent, 2.5%), multiple gestation (3.5%), and inadequate weight gain. Of interest is that there was no significant increase in preeclampsia, pyelonephritis, smoking, or alcohol or substance abuse. Although the present study supports the increasing risk of antepartum complications with increasing maternal weight, the list of antepartum complications is all-encompassing and does not identify specific antepartum complications for which the obese gravid woman is at greater risk.

The present study looks at perinatal mortality in relation to excess maternal weight. A number of previous studies have shown an associated increased perinatal mortality in the obese patients[2-4, 7]; others have not.[8, 9] In this study, if patients with and without antepartum complications are pooled, perinatal mortality increased with excess maternal weight. In the absence of antepartum complications, however, there was no significant difference in perinatal mortality among the varying weight groups. Although this is reassuring to the gravid woman without antepartum complications, it is of note that perinatal mortality in this group of patients was almost twice that of the normal-weight groups without antepartum complications and thus may be clinically significant to the obstetricians taking care of the patients. Since it is also impossible to predict which obese patients will develop antenatal complications, all patients should be considered high risk.

The authors showed an increased incidence of primary cesarean section among all obese patients, regardless of the presence or absence of antepartum complications. Increased operative delivery has been seen in prior studies[1-6] and not in others.[8, 9] From the present study, it is apparent that 17.2% of patients with obesity require a cesarean section. The implications of this are significant, since cesarean section presents a significant hazard to the obese patient and her infant. There is no question that cesarean section in these patients poses both surgical and anesthetic difficulties. Since the obese are also at higher risk for medical complications such as hypertension, toxemia, and diabetes, operative risks are further increased. Additionally, the obese are more prone to postoperative complications such as thromboembolism, pulmonary atelectasis, pneumonia, wound infection, and dehiscence. Sicuranza and Tisdall[10] reviewed their experience with cesarean section in the massively obese (24 patients weighing ≥114 kg). A majority of the patients had multiple indications for surgical delivery, with coexisting diabetes and toxemia. A large infant was a constant finding. The incidence of complications was 17%, but no serious complications were encountered. Attention to prenatal care, prepartum hospitalization, detailed operative technique, careful anesthesia, prophylactic antibiotics, and early ambulation appear to improve maternal outcome. Hodgkinson and Husain[11] likewise reviewed cesarean section in eight patients weighing 150 kg. Six of eight patients had essential hypertension and one had diabetes mellitus. Extradural anesthesia was used in three and general anesthesia in five. They reported in detail on one patient who developed persistent hypotension associated with cephalad retraction of the panniculus during operation under extradural anesthesia. Of the five patients receiving general anesthesia, two became hypertensive during intubation and one developed acute pulmonary edema following removal of the tracheal tube. Postoperative complications were seen in three patients (one minor wound infection, one pulmonary edema, and one abdominal dehiscence). The risks of cesarean section in the obese and the detailed care necessary to diminish them have been reviewed by Gross.[12]

The authors have shown an increasing mean infant birth weight with increasing maternal weight in patients both with and without antepartum complications. This observation has been noted in prior reports.[2-9] It has been postulated that the increase in large infants may be the reason for the increased incidence of primary cesarean section. However, the mean weights of the infants in the obese group in this study are not excessively large. A few earlier reports do not substantiate an increased incidence of cephalopelvic disproportion[2,6] but the majority of reports, including the present one, do not detail the indications for cesarean section.

In summary, this well-designed and well-conducted study objectively reconfirmed the hazards of obesity in pregnancy.

In closing, I would like to ask the authors a few questions: (1) What were the indications for cesarean section in this study? (2) What were the problems or complications associated with the cesarean sections? (3) Are there any recommendations you would make to the obstetrician who finds an obese or morbidly obese woman in his practice?

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DR. FIROOZ BANOONI, Southfield, Michigan. My question is whether the basic classification was at the onset of pregnancy or at the time of delivery. Did the amount of weight that the patient gained during pregnancy make any difference? I believe a gain of 50 pounds during pregnancy could move the patient from one class to the other.

DR. RICHTER (Closing). I can answer the question about the relative distribution of antepartum complications by weight, by telling you that, as expected, in the obese and the morbidly obese groups, the incidence of chronic hypertension and diabetes was very high. In fact, they were the two most common complications, whereas in the normal-weight and the underweight groups these two complications ranked sixth and seventh on the list of complications.

In the underweight group and normal-weight group anemia is a much more frequent complication than in the obese group.

This difference in distribution of complications is one of the postulated reasons the obese gravid woman has a higher incidence of perinatal mortality with complications.

Dr. Varner's question about intrapartum complications cannot be answered from our data. Those data were not available to us. Nor did we know what the indications were for cesarean section.

Concerning the question about recommendations, we have no specific recommendations other than what is obvious in that obese gravid women, since they have a higher incidence of hypertension and diabetes, ought to be screened particularly closely for these. But, at least in our practice, we screen everybody for these diseases, so we do not treat the obese gravid woman any differently than the nonobese gravid woman.

There is some indication in underweight patients, not from our data but from other studies, that food supplementation for people who have a poor diet can increase the fetal weight at delivery. Whether this will change the perinatal outcome we do not know.

The final question pertained to how we classify the pateints. It was done on the basis of prepregnant weight, and that, in fact, explains why so many patients were dropped out of the data, because the prepregnant weight was not always available.

We do not have data on how much weight each of these patients gained during pregnancy.

ITEMS

Announcements of major meetings and other significant activities must be received at least 8 weeks before the desired month of publication. All announcements carry a charge of $45.00 U.S. and the fee must accompany the request to publish. Information will be limited to title of meeting, date, place, and an address to obtain further information. Send announcements and payment, payable to this JOURNAL, to The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63146.

Advanced Ultrasound Seminar—Tenth Anniversary, June 13-15, 1985, Winston-Salem, North Carolina. For further information contact: Dr. James F. Martin, Director, Center of Medical Ultrasound, Bowman Gray School of Medicine, 300 South Hawthorne Road, Winston-Salem, NC 27103. Tel.: (919) 748-4505.

The Mt. Sinai Medical Center of Cleveland Fifth Annual Workshop in Fertility Microsurgery Including In Vitro Fertilization, The Mt. Sinai Medical Center, Cleveland, Ohio. Basic Course: September 9-11, 1985. Advanced Course: September 12-14, 1985. For further information contact: Dr. James M. Goldfarb, The Mt. Sinai Medical Center, University Circle, Cleveland, OH 44106.

London and Paris Fall Ultrasound—Obstetrics and Gynecology, London, England, September 20-25, 1985; Paris, France, September 25-29, 1985. For further information contact: Secretary, Fall Ultrasound Symposia, Medical Seminars International, West Park Medical Office Building, 22135 Roscoe Blvd., #104, Canoga Park, CA 91304. Tel.: (818) 340-0580, ext. 280.

Birth Defects Symposium XVI, Genetic Disease Screening and Management, September 30–October 1, 1985, Albany Hilton Hotel, Albany, New York. For further information contact: Thomas P. Carter, Ph.D., Wadsworth Center for Labs and Research, Rockefeller Empire State Plaza, Albany, NY 12201.

3rd International Symposium on Hormonal Therapy in Climacteric Age: Benefits and Risks, Pisa, Italy, October 20-23, 1985. For further information, please contact the Scientific Secretariat: Dr. V. M. Jasonni or Dr. G. B. Melis, Clinica Ostetrica e Ginecologica, Universita degli Studi di Pisa, Via Roma 67, 56100 Pisa, Italy.

Specialty Review in Obstetrics and Gynecology, October 28–November 2, 1985, Chicago, Illinois. For further information contact: Dick Nelson, Course Manager, The Cook County Graduate School of Medicine, 707 South Wood St., Chicago, IL 60612. Tel.: (312) 633-2600.

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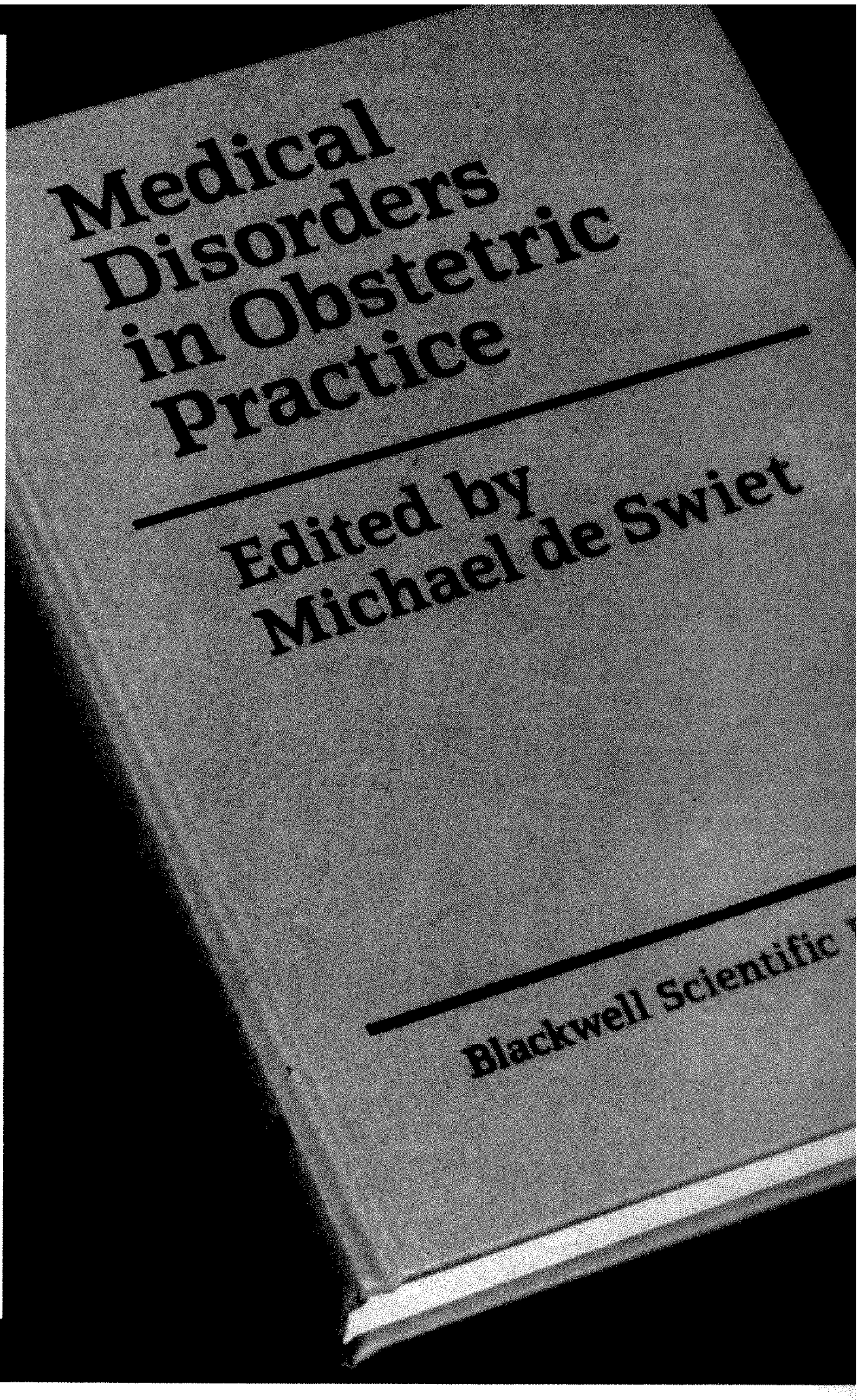
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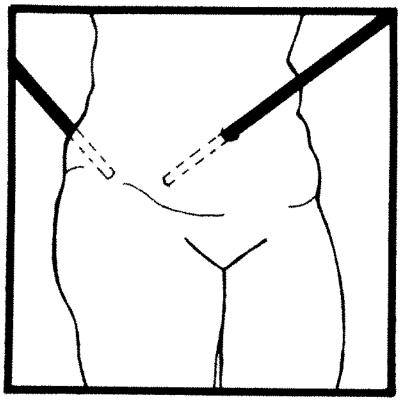

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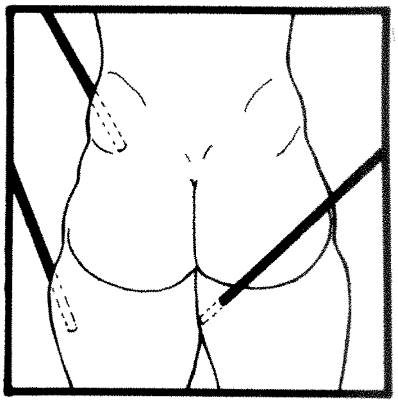

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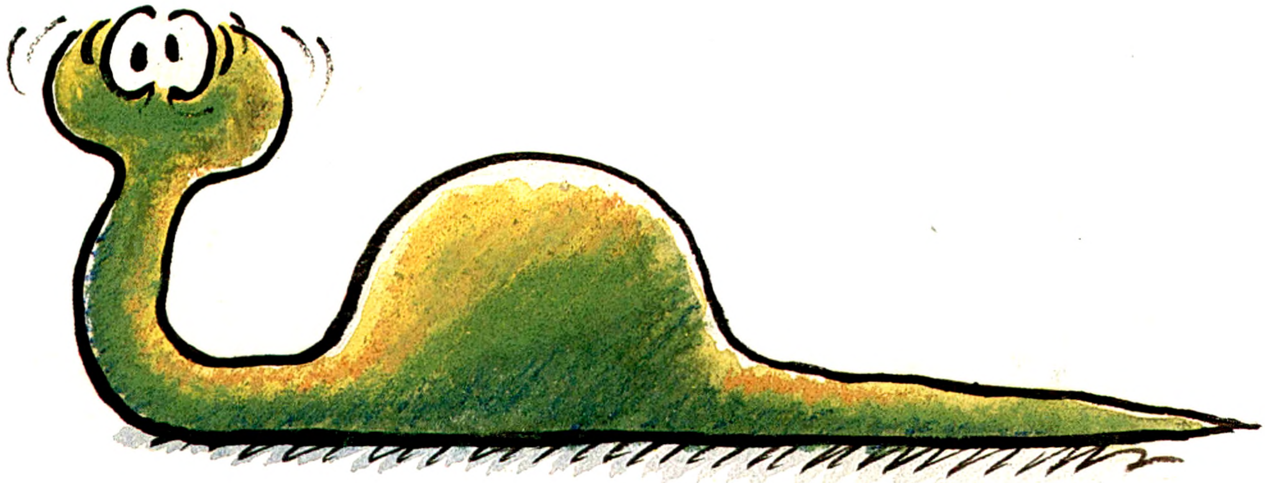

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WARNINGS: Cigarette smoking increases the risk of serious cardiovascular side effects from OC use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use OCs should be strongly advised not to smoke.

The use of OCs is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, liver tumor, gall bladder disease, visual disturbances, fetal abnormalities, and hypertension. Practitioners prescribing OCs should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with OC use is established. One study demonstrated an increased relative risk for fatal venous thromboembolism and several studies demonstrated it for non-fatal venous thromboembolism. They estimate that OC users are 4-11 times more likely than nonusers to develop these diseases without evident cause. One British study reported an excess death rate of 40% in OC users, most of which resulted from cardiovascular disease. Another British study showed a lower death rate in OC users than controls; an increase in cardiovascular deaths was seen but was not statistically significant. A U.S. prospective study failed to disclose increased mortality rates from cardiovascular disorders, but a subset analyzed as a retrospective, case-control study showed significant increases in venous thromboembolism. CEREBROVASCULAR DISORDERS. Two American studies demonstrated an increased relative risk for stroke not shown in prior British studies. In an American study of cerebrovascular disorders in women with and without predisposing causes, relative risk of hemorrhagic stroke was estimated as 2.0 times greater and thrombotic stroke as 4-9.5 times greater in users than nonusers. A British long-term follow-up study reported in 1976 a highly significant association between OC use and stroke. Another study had suggested an association in 1974, but the number of cases was too small to estimate the risk. Subarachnoid hemorrhage has been shown to be increased by OC use in British and American studies. Smoking alone increases incidence of these accidents; smoking and pill use appear to increase risk more than either alone.

MYOCARDIAL INFARCTION (MI). Increased relative risk of MI associated with OC use has been reported. One British study found that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing MI, regardless of OC use. OCs were an additional risk factor. In terms of relative risk, it has been estimated that nonsmoking OC users (smoking is considered a major predisposing condition to MI) are twice as likely to have a fatal MI as nonsmoking nonusers. OC users who are smokers have a 5-fold increased risk of fatal infarction compared to nonsmoking users, and a 10-12-fold increased risk compared to nonsmoking nonusers. The number of cigarettes smoked is important. In determining the importance of these relative risks, baseline rates for various age groups must be considered. (Estimates are based on British vital statistics which show acute MI death rates 2-3 times less than in the U.S. so U.S. death rates could be higher.) Importance of other predisposing conditions in determining relative and absolute risks has not been quantified; other synergistic actions may exist. RISK OF DOSE. Using data from several national adverse reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to estrogen dose in OCs. OCs with 0.1 mg or more of estrogen were associated with a higher risk of thromboembolism than those containing 0.05-0.08 mg but quantity of estrogen may not be the sole factor. This was supported by a U.S. study. A British study found a positive association between dose of progestogen or estrogen and certain thromboembolic conditions. Swedish authorities noted decreased reporting of thromboembolic episodes when higher estrogen preparations were no longer prescribed. Careful epidemiological studies to determine degree of thromboembolic disease risk associated with progestogen-only OCs have not been done. Thromboembolic disease has been reported in women using these products, and they should not be considered free of excess risk. PERSISTENCE OF RISK. Two studies have suggested an increased risk may persist for 6 years after discontinuation of OC use for cerebrovascular disease and 9 years for MI; another study suggested the persistence of risk for subarachnoid hemorrhage. ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES. A large British prospective study estimated mortality rate per 100,000 women per year from circulatory system diseases for OC users and nonusers according to age, smoking habits, and duration of use. The overall annual excess death rate for OC users was estimated to be 20/100,000 (ages 15-34–5/100,000; ages 35-44–33/100,000; ages 45-49–140/100,000). Risk is concentrated in long-term users and in smokers, and may persist after OC discontinuation. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all occurred in women 35 or older. An update provided the following rates: ages 15-34–1/6700 for nonsmokers and 1/2000 for smokers; ages 45 and over–1/2500 for nonsmokers and 1/500 for smokers. Risk appeared to increase with parity, but not with duration of use. Until more women under 35 with continuous use for 5 or more years are available, it is not possible to assess relative risk for this age group. Data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. Estimates include combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease for OCs) plus risk attributable to pregnancy or abortion if the method fails (which varies with the effectiveness of the contraceptive method). The study concluded that mortality associated with all contraceptive methods is below that of childbirth, except for OCs in women over 40 who smoke. (Rates given for pill only/smokers for each age are for smokers as a class. For "heavy" smokers (more than 15 cigarettes a day), the rates would be about double; for "light" smokers (less than 15), about half.) The lowest mortality is with the condom or diaphragm backed up by early abortion. The study also concluded that OC users who smoke, especially over 30, have greater mortality risk than OC users who do not smoke.

Risk of thromboembolic and thrombotic disease associated with OCs increases with age after 30 and for MI is further increased by hypertension, hyperlipidemias, obesity, diabetes, or history of preeclamptic toxemia, and especially by smoking. The following chart gives a gross estimate of risk of death from circulatory disorders associated with OC use.

SMOKING HABITS AND OTHER PREDISPOSING
CONDITIONS–RISK ASSOCIATED WITH USE OF OCs

Age	Below 30	30-39	40 +
Heavy smokers	C	B	A
Light smokers	D	C	B
Nonsmokers (no predisposing conditions)	D	C,D	C
Nonsmokers (other predisposing conditions)	C	C,B	B,A

A–Use associated with very high risk.
B–Use associated with high risk.
C–Use associated with moderate risk.
D–Use associated with low risk.

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, discontinue OC immediately. A 4-6 fold increased risk of post-surgery thromboembolic complications has been reported in OC users. If feasible, discontinue OCs at least 4 weeks before surgery associated with increased risk of thromboembolism or prolonged immobilization. Before resuming OC after major surgery or bedrest, balance risks of post-surgery thromboembolic complications with contraceptive needs. Data suggest varicose veins substantially increase risk of superficial venous thrombosis of the leg, the risk depending on the severity of the varicosities. 2. *Ocular Lesions:* Neuro-ocular lesions such as optic neuritis or retinal thrombosis have been associated with OC use. Discontinue OC if there is unexplained, sudden, or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions; and institute appropriate diagnostic and therapeutic measures. 3. *Carcinoma:* Long-term continuous administration of natural or synthetic estrogen in certain animals increases certain tumors, benign or malignant, such as breast, cervix, vagina, uterus, ovary, pituitary and liver. Certain synthetic progestogens, none currently in OCs, increase the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studies reported an increased relative risk (3.1-13.9 times) associating endometrial carcinoma with the prolonged use of estrogens in postmenopausal women. One publication reported the first 30 cases submitted to the registry of cases of adenocarcinoma of the endometrium in women under 40 on OCs. Of the adenocarcinomas found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding when OCs were first given, polycystic ovaries), nearly all occurred in women who had used sequential OCs, which are no longer marketed. No statistical association has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only OCs, although individual cases have been reported. Studies have shown no increased risk of breast cancer to OC or estrogen users. One study found no overall increased risk of breast cancer in OC users but a greater risk was suggested for OC users with documented benign breast disease and for long-term (2-4 years) users. Another study found a history of breast cancer among grandmothers or aunts was significantly more frequent among breast cancer patients who had used an OC continuously for one or more years than among nonusers with breast cancer. One other study indicated an increasing risk of breast cancer in women taking menopausal estrogens, which increased with duration of follow-up. One author suggests that extended (over 6 years) OC use prior to first full term pregnancy was associated with a significant relative risk of breast cancer. A reduced occurrence of benign breast tumors in OC users has been well documented. One study reported malignant melanoma more frequently in OC users than controls and suggests an increased incidence of urinary tract and thyroid cancers. A prospective study of women with cervical dysplasia found an increase in severity and conversion to cancer *in situ* in OC users compared to nonusers. This became statistically significant after 3-4 years of use. Nonreversal of dysplasia within the first 6 months of pill use was suggested to predict progression after prolonged exposure. One study disclosed an increased risk of cancer of the cervix (largely carcinoma *in situ*) in OC users under 40, particularly those who had used OCs over 4 years. There have been other reports of microglandular hyperplasia of the cervix in OC users. One study reported an association between OC use and endocervical adenocarcinoma. In summary, there is no confirmed evidence from human studies of increased risk of cancer associated with OCs. Close clinical surveillance of all OC users is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, take appropriate diagnostic measures to rule out malignancy. Monitor OC users with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms with particular care. 4. *Liver Tumors:* Sudden severe abdominal pain or shock may be due to rupture and hemorrhage of a liver tumor. There have been reports associating benign or malignant liver tumors with short-term and long-term OC use. One study reported use of OCs with high hormonal potency and age over 30 may further increase risk of hepatocellular adenoma. Two studies relate risk with duration of use, risk being much greater after 4 or more years of use. Long-term OC users have an estimated annual incidence of hepatocellular adenoma of 3-4/100,000. Although an uncommon lesion, it should be considered in women presenting with an "acute abdomen". The tumor may cause serious or fatal hemorrhage. Patients with liver tumors have demonstrated variable clinical features which may make preoperative diagnosis difficult. Some cases presented because of right upper quadrant masses, while most had signs and symptoms of acute intraperitoneal hemorrhage. Routine radiological and laboratory studies may not be helpful. Liver scans may show a focal defect. Hepatic arteriography may be useful in diagnosing primary liver neoplasm. 5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring:* Use of female sex hormones–estrogenic and progestational agents–during early pregnancy may seriously damage the offspring. Females exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be of the order of 1/1000 exposures or less. Although there is no evidence that OCs further enhance the risk of developing this type of malignancy, such OC users should be monitored with particular care. A high percentage of women exposed to diethylstilbestrol (30-90%) have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are a precursor of vaginal malignancy. Male children so exposed may develop urogenital tract abnormalities. Although similar data are not available on other estrogens, it cannot be presumed that they would not induce similar changes. Increased risk of congenital anomalies, including heart and limb defects, has been reported following use of sex hormones, including OCs, in pregnancy. One case-control study estimated a 4.7-fold increased relative risk of limb-reduction defects in infants exposed *in utero* to sex hormones (OCs, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some exposures involved only a few days of treatment. Data suggest risk of limb-reduction defects in exposed fetuses is somewhat less than 1/1000 live births. In a large prospective study, cardiovascular defects in children born to women who received female hormones, including OCs, during early pregnancy occurred at 18.2/1000 births, compared to 7.8/1000 for children not so exposed *in utero*. These results are statistically significant. A Welsh study found a statistically significant excess of neural tube defects among offspring of prior OC users (within 3 months) than among controls. The incidence of twin births may be increased for women who conceive shortly after discontinuing OC use. In the past, female sex hormones were used during pregnancy in an attempt to treat threatened or habitual abortion. There is evidence that estrogens are ineffective, and there is no evidence from well controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OCs. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OCs is unknown. If the patient has not adhered to the prescribed schedule, consider possible pregnancy at the first missed period (or 45 days from the last menstrual period if progestogen-only OCs are used) and discontinue OC use until pregnancy has been ruled out. For any patient who has missed two consecutive periods, rule out pregnancy before continuing the OC. If pregnancy is confirmed, tell the patient about potential risks to the fetus and discuss advisability of continuing the pregnancy. Women who discontinue OCs to become pregnant should use an alternate form of contraception for a period of time before attempting to conceive. A 3-month period is supported by a study suggesting increased frequency of neural tube defects in women impregnated during the first 3 months after cessation of OC use. Do not use progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding as a pregnancy test. 6. *Gall Bladder Disease:* Studies report increased risk of gall bladder disease in OC or estrogen users. In one study, an increased risk appeared after 2 years of use and doubled after 4-5 years. In another study, an increased risk was apparent between 6 and 12 months. 7. *Carbohydrate and Lipid Metabolic Effects:* Because a decrease in glucose tolerance has been observed in a significant percentage of patients on OCs, prediabetic and diabetic OC users should be carefully observed. An increase in triglycerides and total phospholipids has been observed in OC users but its clinical significance is unknown. 8. *Elevated Blood Pressure:* An increase in blood pressure has been reported with OC use. Hypertension may occur within a few months of beginning OCs. In the first year of use, incidence of hypertension may be no higher in OC users than in nonusers. Incidence in users increases with exposure and in the fifth year of use is 2.5-3 times that in the first year. Age is strongly correlated with hypertension in OC users. Women with a history of elevated blood pressure (hypertension), preexisting renal disease, history of toxemia or elevated blood pressure during pregnancy, familial tendency to hypertension or its consequences," or history of excessive weight gain or fluid retention during the menstrual cycle may be more likely to develop elevated blood pressure when given OCs and should be monitored closely. Even though elevated blood pressure may remain within the "normal" range, closely watch elevations, particularly for women with other risk factors for cardiovascular disease or stroke. High blood pressure may or may not persist after OC discontinuation. 9. *Headache:* Discontinue OC and evaluate the cause of onset or exacerbation of migraine or development of a new pattern of headache which is recurrent, persistent, or severe. 10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and missed menses often make users discontinue OCs. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, consider nonfunctional causes. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, use adequate diagnostic measures to rule out pregnancy or malignancy. If pathology has been excluded, time or another formulation may solve the problem. While potentially useful in minimizing menstrual irregularity, change to an OC with a higher estrogen content only if necessary since this may increase the risk of thromboembolic disease. Women with a history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may tend to remain anovulatory or to become amenorrheic after OC discontinuation. Women with these preexisting problems should be advised of this and encouraged to use other contraceptive methods. Post-use anovulation, possibly prolonged, may occur in women without previous irregularities. A higher incidence of galactorrhea and of pituitary tumors (e.g., adenomas) has been associated with amenorrhea in former users compared with nonusers. One study reported a 16-fold increased incidence of pituitary prolactin-secreting tumors among patients with postpill amenorrhea when galactorrhea was present. 11. *Infertility:* There is evidence of impairment of fertility in women discontinuing OCs in comparison with other contraceptive methods, which appears to be independent of duration of use. While impairment diminishes with time, there is an appreciable difference in the results in nulliparous women for OC and other groups 30 months after discontinuation of birth control. For parous women the difference is not apparent 30 months after cessation of contraception. 12. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in OC failure. In progestogen-only OC failures, the ratio of ectopic to intrauterine pregnancies is higher than in nonusers, since the drugs are more effective in preventing intrauterine than ectopic pregnancies. 13. *Breast Feeding:* OCs in the postpartum period may interfere with lactation by decreasing quantity and quality of breast milk. A small fraction of OC hormonal agents has been identified in milk of mothers receiving OCs. Effects, if any, on the breast-fed child have not been determined. If feasible, defer OC use until the infant has been weaned. **Precautions** *GENERAL* 1. Take a complete medical and family history before starting OCs. Pretreatment and periodic physical exams should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant lab tests. As a general rule, OCs should not be prescribed for longer than 1 year without another physical. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may enlarge. 3. Observe patients with a history of psychic depression and discontinue OCs if depression recurs to a serious degree. Patients becoming significantly depressed while taking OCs should stop the OC and use an alternate method of contraception to determine whether the symptom is drug related. 4. OCs may cause some fluid retention. Prescribe with caution, and only with careful monitoring, in patients with conditions that might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma or cardiac, hepatic or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while using OCs. Discontinue OC if jaundice develops. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. OC users may have disturbances in normal tryptophan metabolism that may result in a relative pyridoxine deficiency. The clinical significance is unknown. 8. Serum folate levels may be depressed by OC use. Since the pregnant woman is predisposed to folate deficiency and incidence of folate deficiency increases with increasing gestation, if a woman becomes pregnant shortly after stopping OCs, she may have a greater chance of developing folate deficiency and related complications. 9. Advise the pathologist of OC use when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing OCs. For example: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. f. Increased phospholipids and triglycerides. g. Temporarily decreased glucose tolerance. 11. Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist and temporary or permanent cessation of wear considered. DRUG INTERACTIONS. OCs may be less effective and there may be increased breakthrough bleeding from interactions with rifampin, isoniazid, ampicillin, tetracycline, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, analgesics, tranquilizers, antimigraine preparations, and antihistamines. OCs may alter effectiveness of such other drugs as oral anticoagulants, anticonvulsants, tricyclic antidepressants, antihypertensive agents (e.g., guanethidine), vitamins, hypoglycemic agents, tranquilizers, hypnotic preparations, and theophylline. *CARCINOGENESIS* See Warnings. *PREGNANCY* Pregnancy category X. See Contraindications and Warnings. *NURSING MOTHERS* See Warnings. **Adverse Reactions** An increased risk of the following serious adverse reactions has been associated with OC use (see Warnings): thrombophlebitis, thrombosis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, mesenteric thrombosis, liver tumors, cerebral hemorrhage, hypertension, gall bladder disease, congenital anomalies, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, Raynaud's disease, arterial thromboembolism. The following adverse reactions have been reported in OC users and are believed to be drug related: bleeding irregularities (breakthrough bleeding, spotting, missed menses during treatment, amenorrhea after treatment), gastrointestinal symptoms, (nausea, vomiting, bloating, abdominal cramps), dysmenorrhea, infertility after discontinuance of treatment, edema, chloasma or melasma which may persist after drug is discontinued, breast changes (tenderness, enlargement, and secretion), intolerance to contact lenses, changes in corneal curvature (steepening), change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution of lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, prolactin-secreting pituitary tumors, chilblains. The following adverse reactions have been reported in OC users and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of hair, erythema multiforme, erythema nodosum, hermorrhagic eruptions, vaginitis, porpyhria, impaired renal function, malignant nephrosclerosis (hemolytic uremic syndrome). **Information for the Patient** (See Patient Package Insert).

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Contents

June 1
1985

CLINICAL SECTION

Clinical Opinion

Vaginitis 247
Eduard G. Friedrich, Jr., M.D.
Gainesville, Florida

Clinical Articles

Preventing febrile complications of suction curettage abortion 252
Tai-Keun Park, M.D., M.P.H., Ph.D., Melinda Flock, M.S.P.H., Kenneth F. Schulz, M.B.A., and David A. Grimes, M.D.
Atlanta, Georgia

(Contents continued on page 5A)

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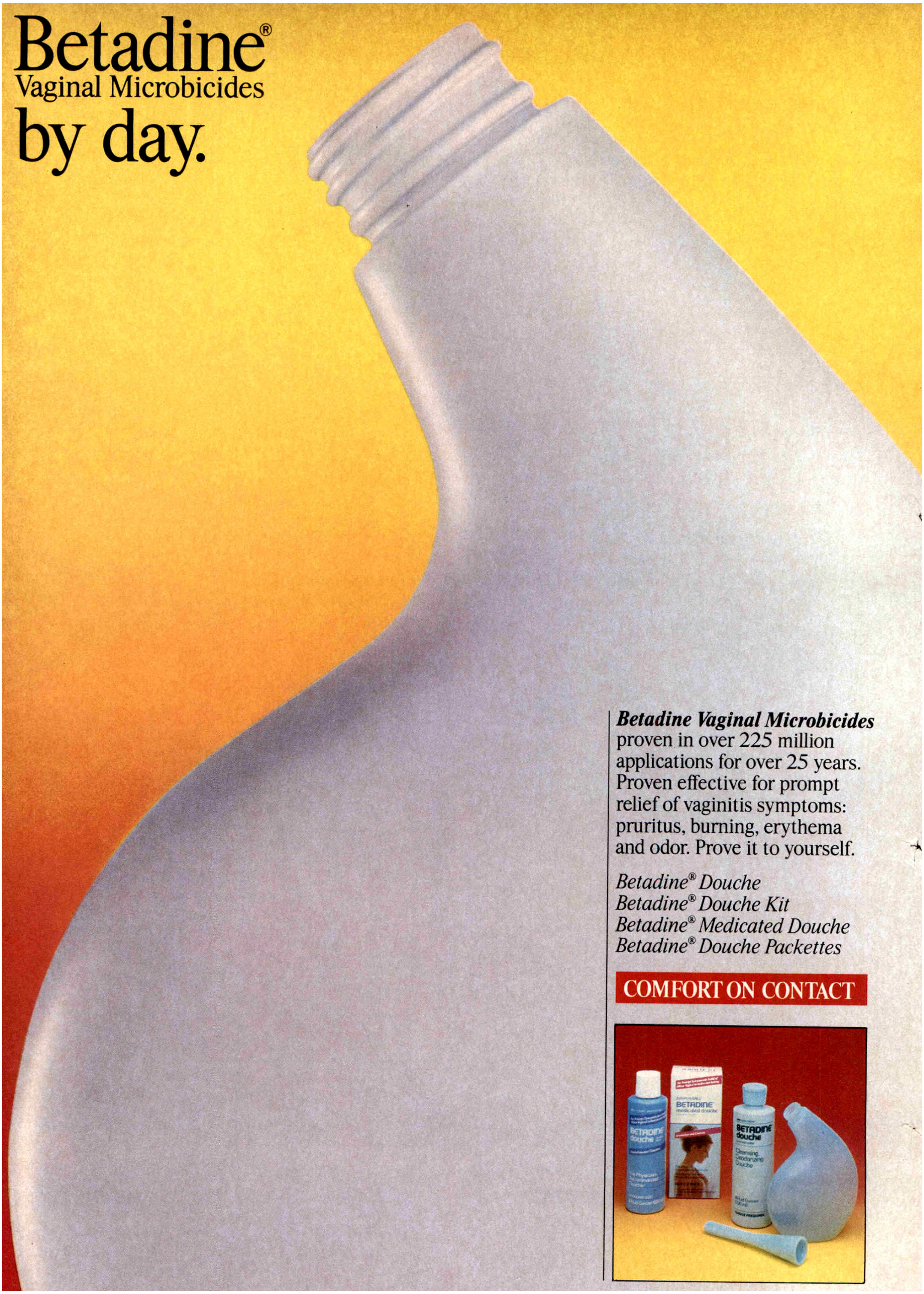

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COMFORT ON CONTACT

Contents continued from page 3A

The relationship between perinatal hypoxia and newborn encephalopathy 256
J. A. Low, M.D., R. S. Galbraith, M.D., D. W. Muir, Ph.D.,
H. L. Killen, R.N., E. A. Pater, R.N., and E. J. Karchmar, B.A.
Kingston, Ontario, Canada

Superficial laser vulvectomy. II. The anatomic and biophysical principles permitting accurate control over the depth of dermal destruction with the carbon dioxide laser 261
Richard Reid, M.D., Edna A. Elfont, Ph.D., Richard M. Zirkin, M.D., and
Terry A. Fuller, Ph.D.
Detroit, Michigan

Continuous long-term intravenous β-sympathomimetic tocolysis 271
Washington C. Hill, M.D., Michael Katz, M.D., John L. Kitzmiller, M.D., and
Pamela J. Gill, R.N., M.S.N.
San Francisco, California

Immunoperoxidase localization of chlamydial antigens in acute salpingitis 275
Barbara Winkler, M.D., Werner Reumann, M.D., Masaru Mitao, M.D., Leza Gallo, M.D.,
Ralph M. Richart, M.D., and Christopher P. Crum, M.D.
New York, New York

***Chlamydia trachomatis* isolation in patients with endometritis after cesarean section** 278
Jorge D. Blanco, M.D., Karen C. Diaz, M.D., Kathleen A. Lipscomb, R.N., Donald Bruun,
and Ronald S. Gibbs, M.D.
San Antonio, Texas

Prevalence and manifestations of endometritis among women with cervicitis 280
Jorma Paavonen, M.D., Nancy Kiviat, M.D., Robert C. Brunham, M.D.,
Claire E. Stevens, M.A., P.A., Cho-Chou Kuo, M.D., Walter E. Stamm, M.D.,
Ari Miettinen, M.D., Michael Soules, M.D., David A. Eschenbach, M.D., and
King K. Holmes, M.D., Ph.D.
Seattle, Washington, and Tampere, Finland

***Actinomyces* and the intrauterine contraceptive device: Aspects of the fluorescent antibody stain** 287
Leo Pine, Ph.D., Ernest M. Curtis, M.D., and June M. Brown, B.S.
Atlanta, Georgia

Renal vein thrombosis following puerperal ovarian vein thrombophlebitis 290
Robert R. Bahnson, M.D., Earl F. Wendel, M.D., and Robert L. Vogelzang, M.D.
Chicago, Illinois

(Contents continued on page 7A)

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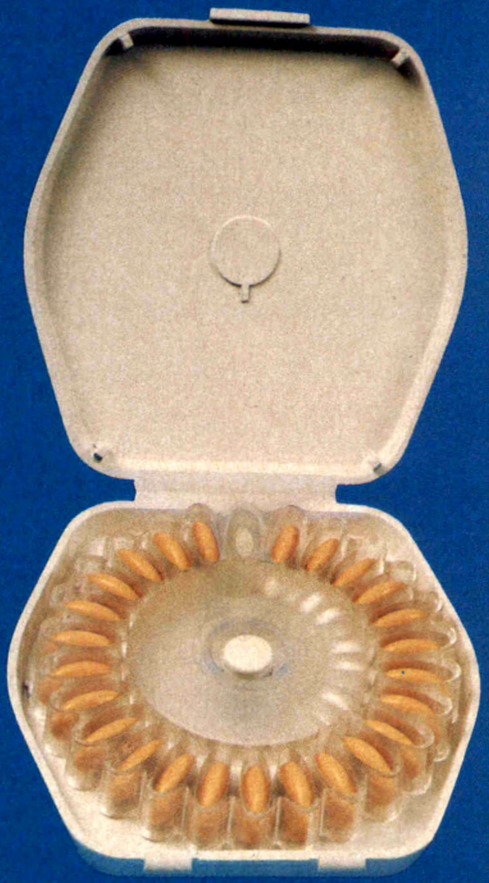

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Contents continued from page 5A

Interval tubal sterilization in obese women—An assessment of risks 292
I-cheng Chi, M.D., Dr.P.H., and Lynne Wilkens, M.S.P.H.
Research Triangle Park, North Carolina

Intrapartum external cephalic version 297
James E. Ferguson II, M.D., and Donald C. Dyson, M.D.
Stanford and Santa Clara, California

Doubling times of human chorionic gonadotropin increase in early viable intrauterine pregnancies 299
Donald E. Pittaway, M.D., Ph.D., Rodney L. Reish, M.S., and Anne Colston Wentz, M.D.
Winston-Salem, North Carolina, and Nashville, Tennessee

Syndrome of camptodactyly, ankyloses, facial anomalies, and pulmonary hypoplasia (Pena-Shokeir syndrome): Obstetric and ultrasound aspects 303
Lewis Shenker, M.D., Kathryn Reed, M.D., Caroline Anderson, R.D.M.S.,
Lynn Hauck, M.A., and Ronald Spark, M.D.
Tucson, Arizona

Arrested puberty associated with a Sertoli-Leydig cell tumor 308
Amalia C. Kelly, M.D., Michael A. Feinman, M.D., and Nabil Husami, M.D.
New York, New York

Long-term survival rates with various chemotherapeutic regimens in Stages III and IV ovarian adenocarcinoma 310
J. J. Barlow, M.D., S. B. Lele, M.D., and L. J. Emrich, Ph.D.
Buffalo, New York

Effect of treatment with sodium valproate on plasma adrenocorticotropic hormone and cortisol concentrations in pregnancy 315
Christos G. Hatjis, M.D., James C. Rose, Ph.D., Charles Pippitt, M.D., and
Melissa Swain, R.N.
Winston-Salem, North Carolina

Unsuccessful treatment of fetal immunologic thrombocytopenia with dexamethasone 316
Chang-Sheng Yin, M.D., and James R. Scott, M.D.
Salt Lake City, Utah, and Taipei, Taiwan, Republic of China

Current Development

Prostacyclin and thromboxane in gynecology and obstetrics 318
O. Ylikorkala, M.D., and U.-M. Mäkilä, M.D.
Helsinki and Oulu, Finland, and Washington, D.C.

(Contents continued on page 8A)

Contents continued from page 7A

BASIC SCIENCE SECTION

Hemodynamic observations in severe preeclampsia complicated by pulmonary edema 330
Thomas J. Benedetti, M.D., Richard Kates, M.D., and Virginia Williams, M.D.
Seattle and Spokane, Washington

Preeclampsia: An imbalance in placental prostacyclin and thromboxane production 335
Scott W. Walsh, Ph.D.
East Lansing, Michigan

The relationship of fetal plasma protein concentration and hemoglobin level to the development of hydrops in rhesus isoimmunization 341
K. H. Nicolaides, M.D., J. C. Warenski, M.D., and C. H. Rodeck, M.D.
London, England

The role of transferrin and ferritin in the fetal-maternal-placental unit 344
Teruaki Okuyama, M.D., Tetsuo Tawada, M.D., Hiroshi Furuya, M.D., and
Claude A. Villee, Ph.D.
Boston, Massachusetts, and Tokyo, Japan

Effects of maternal oxygen administration on fetal oxygenation during reductions in umbilical blood flow in fetal lambs 351
Daniel I. Edelstone, M.D., Benjamin B. Peticca, M.D., and Lee J. Goldblum, M.D.
Pittsburgh, Pennsylvania

CORRESPONDENCE

Ultrasound diagnosis of meconium-stained amniotic fluid F. W. S. Wong, M.Med., E. P. L. Loong, M.B., and A. M. Z. Chang, Ph.D. *Shatin, Hong Kong* 359

Reply Beryl Benacerraf, M.D., Mary Gatter, M.D., and Fruma Ginsburgh, M.D. *Boston, Massachusetts* 359

Natural killer cell activity during pregnancy Carlos Labarrere, M.D. *Buenos Aires, Argentina* 359

Reply Kunihiro Okamura, M.D. *Sendai, Japan* 360

Sonographic appearance of the ovarian thecoma Joseph S. K. Woo, M.B., B.S., and A. Ghosh, M.B., B.S. *Hong Kong* 361

Hormone levels and premenstrual syndrome A. J. Martin, M.B. *Southhampton, England* 361

Reply B. Faratian, M.D., P. M. S. O'Brien, M.D., and G. M. Filshie *Nottingham, England* 362

Contents

Sinusoidal fetal heart rate and butorphanol administration Selman I. Welt, M.D. *Johnson City, Tennessee* 362

Cesarean section delivery and future childbearing Bonny T. Lee, B.S.N. *Columbus, Georgia* 363

Genital chlamydial infection and cervical cancer Benjamin Piura, M.D., Batia Sarov, M.P.H., and Israel Sarov, Ph.D. *Beer-Sheva, Israel* 363

Reply Richard Reid, M.D. *Detroit, Michigan* 364

IN MEMORIAM

Howard C. Taylor, Jr., M.D. 365

BOOKS

Books received 367

ITEMS

Items 368

Information for authors on pages 21A and 22A

Index to advertisers on page 32A

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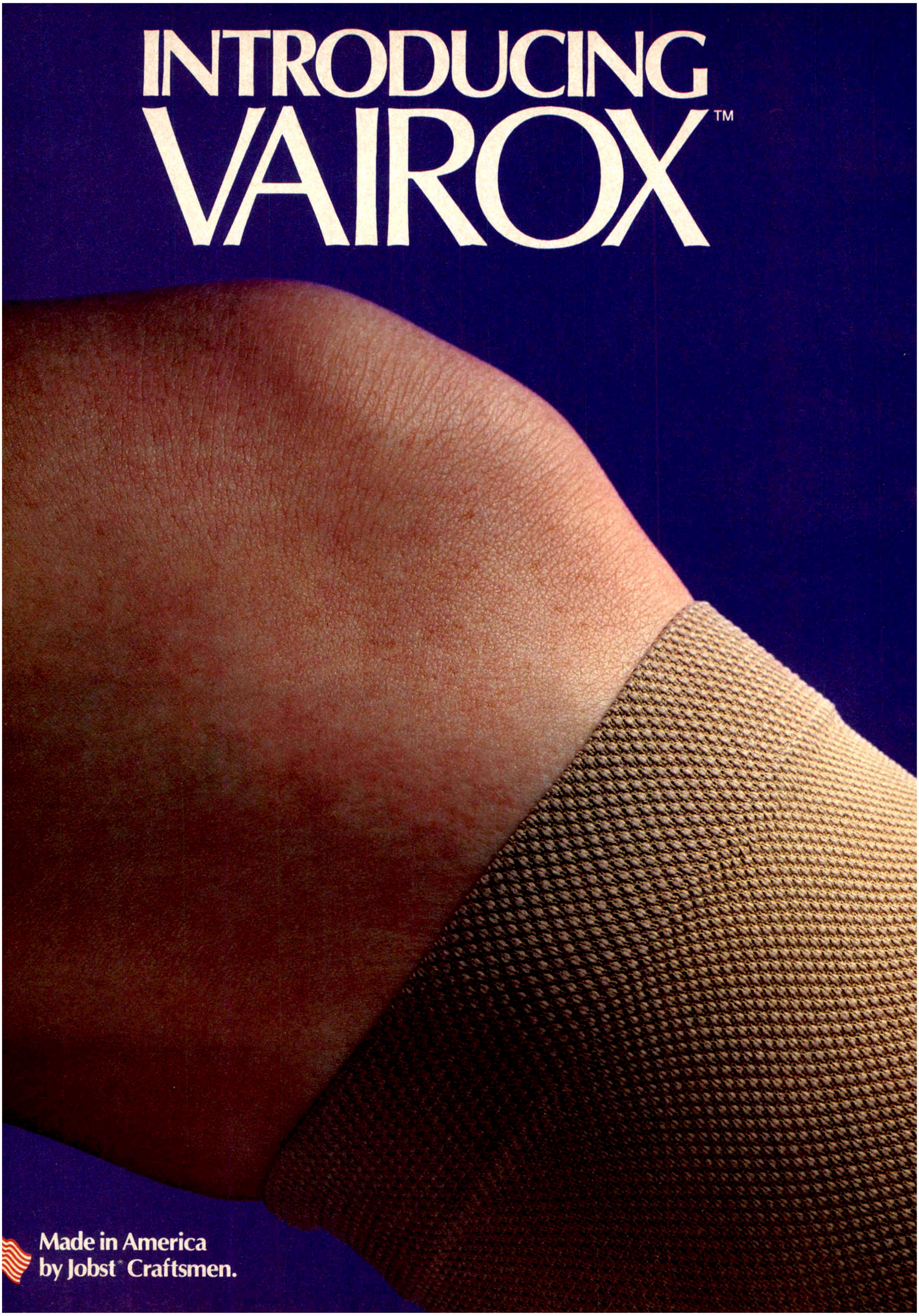

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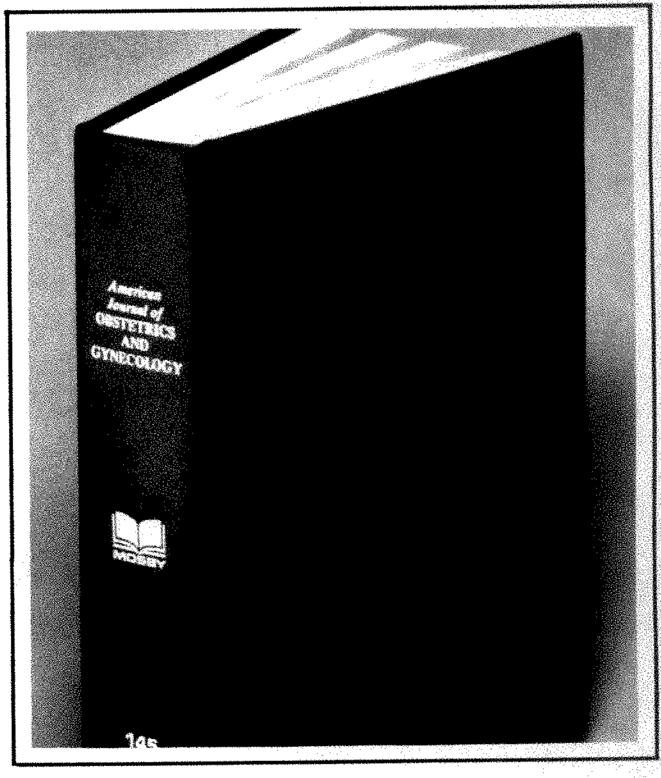

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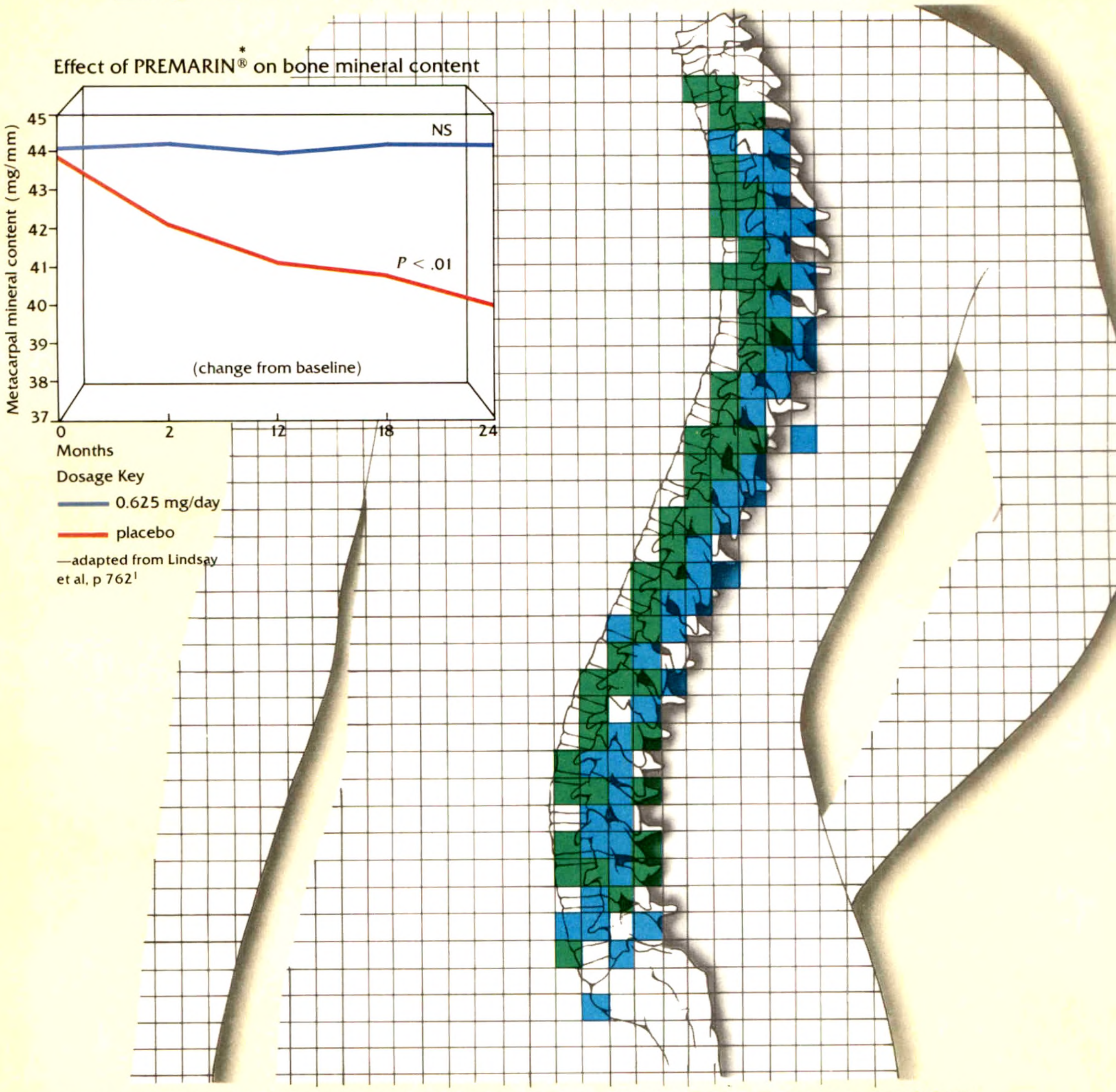

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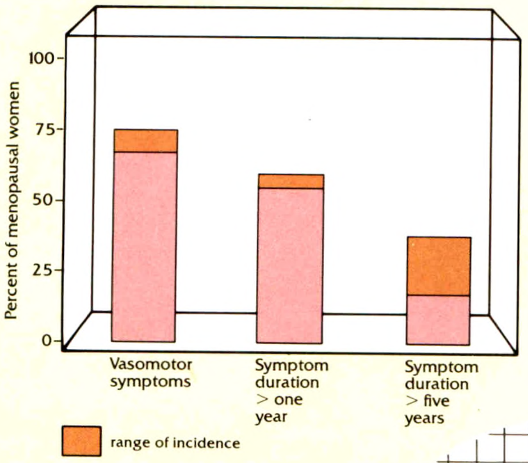
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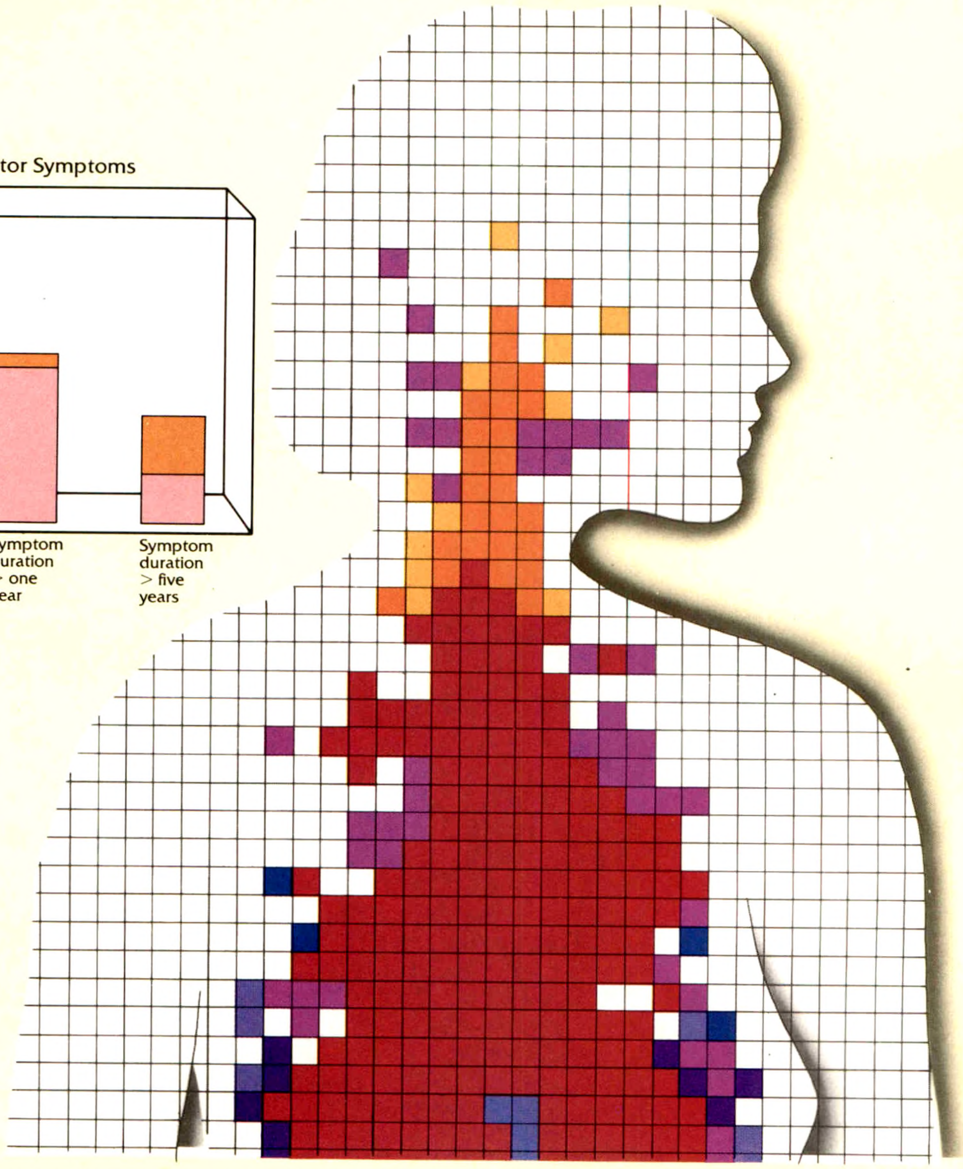
—adapted from Judd, p 20[4]



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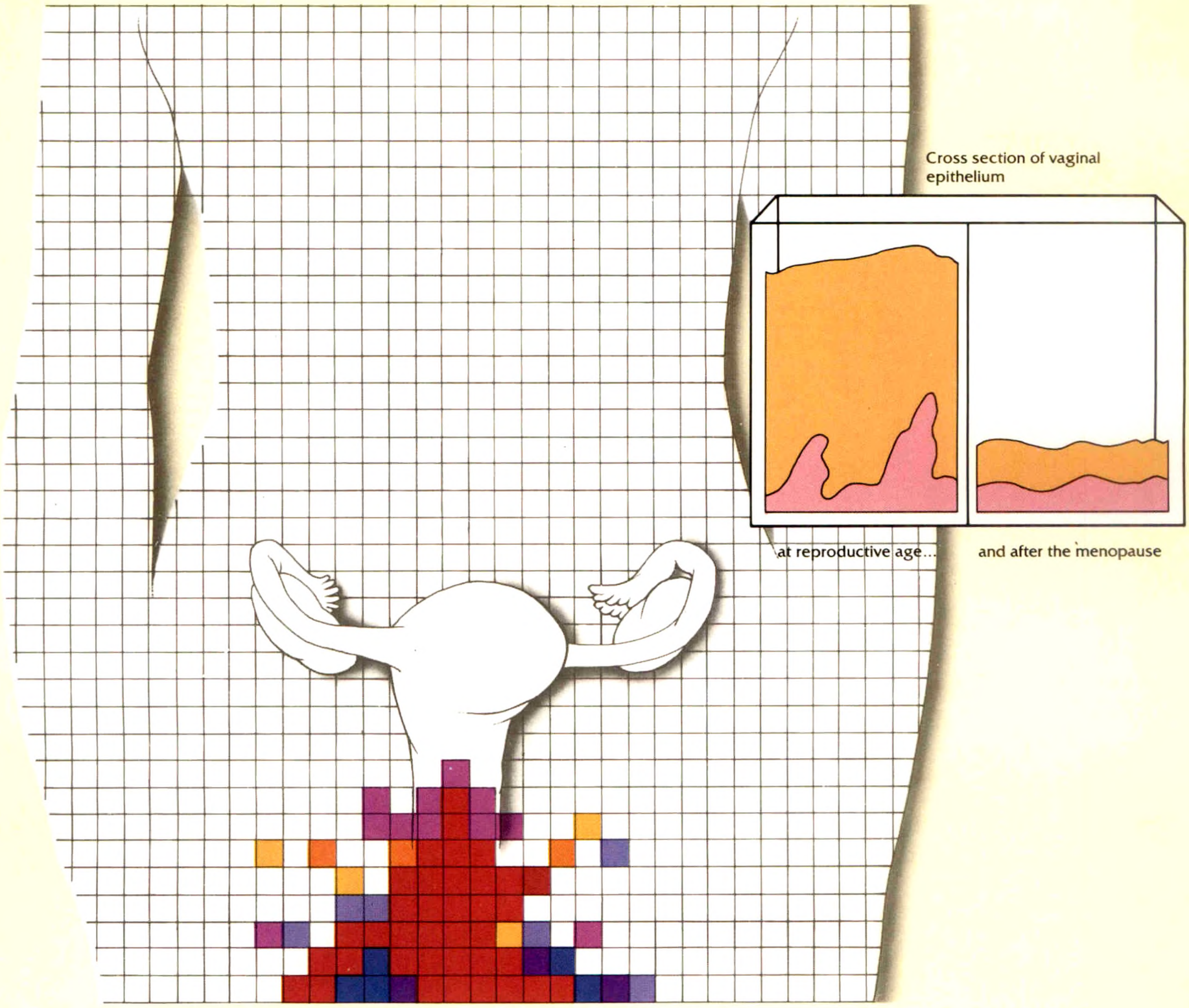

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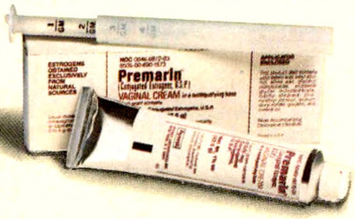

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PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream No. 872 Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

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References: 1. Lindsay R, Hart DM, Clark DM: The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstet Gynecol* 1984;63:759-763. **2.** Katz WA: *Rheumatic Diseases: Diagnosis and Management*. Philadelphia, JB Lippincott Co, 1977, p 672. **3.** Reese WD: A better way to screen for osteoporosis. *Contemp Ob/Gyn* 1983;22(November):116-131. **4.** Judd HL: After the menopause. *Transition* 1983;1:19-30. **5.** Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. **6.** Meldrum DR: The pathophysiology of postmenopausal symptoms. *Sem Reprod Endocrinol* 1983;1(February):11-17.

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CLINICAL SECTION

Clinical Opinion

Vaginitis

Eduard G. Friedrich, Jr., M.D.
Gainesville, Florida

Vaginitis is one of the most common complaints of women in the United States today. About 90% of patients with this problem suffer from infection of the vagina caused by *Candida, Gardnerella,* or *Trichomonas.* The diagnosis and effective treatment of these common infections depend on accurate identification of the entity, effective specific therapy, and restoration of the normal ecosystem of the vagina. At the same time women should be made aware that not all discharge means infection and that any attempts at self-treatment may only worsen their condition. Proper hygiene habits, dietary control, and management of stress are all helpful factors in the control of recurrent vaginal infections. (AM J OBSTET GYNECOL 1985;152:247-51.)

Key words: Vaginitis, *Candida, Gardnerella, Trichomonas*

Vaginitis is one of the most common reasons for physician consultation in the United States today. About nine of ten patients with this problem suffer from infection of the vagina by *Candida* species, *Gardnerella,* or *Trichomonas,* either alone or in combination. Besides being a source and a means of transmission of the organism, such infections are encouraged by or result in a change in the normal vaginal ecology.[1]

In some women the vaginal ecosystem is quite stable. The normal acidogenic flora, mostly lactobacilli, competitively inhibit the growth of pathogens through maintenance of an acidic environment. However, a few women have such a delicately balanced ecosystem that even temporary changes in vaginal pH are sufficient to allow pathogenic organisms (usually present in the endocervix) to overwhelm the protective flora.[2] Such patients complain of "infection" from their sexual partners after each episode of coitus. In such circumstances, when no sexually transmitted diseases can be found, it is likely that the 6- to 8-hour period of vaginal alkalinity produced by retention of buffered semen has simply allowed pathogenic flora to gain control. A postcoital vinegar douche will usually prevent continued episodes.

The diagnosis and management of the common vaginitides (*Candida, Gardnerella,* and *Trichomonas*) depend on: (1) accurate identification of the causative agent, (2) selection and administration of effective specific therapy, and (3) restoration of the normal ecosystem. When a patient presents with a "perplexing" case of otherwise straightforward vaginitis, it is usually because one of these basic steps has been overlooked.

Microscopic wet smears of the vaginal secretions in physiologic saline solution and in 10% potassium hydroxide must be made and carefully examined. They are as essential as the measurement of the vaginal pH, which is easily accomplished with Nitrazine paper. After insertion of a dry speculum (tap water rinsing of the speculum may give a false pH reading), a drop of saline solution is placed on one microscopic slide and a drop of potassium hydroxide on another. With the use of the paddle end of a wooden Papanicolaou smear blade, some typical discharge is sampled from the vaginal walls or pool. I deliberately avoid contact with cervical mucus. The secretions are then gently mixed with the drop of saline solution first and then scraped, if necessary, onto the potassium hydroxide slide. A cover

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Table I. Major categories of vaginitides

	Candida			
	Albicans	Glabrata	Gardnerella	Trichomonas
Symptom	Itch	Burn	Odor	Discharge
Mucosal erythema*	+ + +	+	None	Variable
pH	4-5	4-5	5-6	6-7
Wet smear	Budding filaments	Spores only	Clue cells	Many white blood cell protozoa

*Degree of severity: +, mild; + + +, severe.

slip is immediately placed on top of each drop. A piece of Nitrazine paper is then used to sample the pH of the discharge in the vaginal pool. If only small amounts are present on the vaginal walls, a clear wooden spatula can be used to press the paper against the mucosa. The cervical mucus must be avoided, since it is always relatively alkaline.

The results from these simple techniques must be combined with a careful history of the main symptom and its course as well as the gross appearance of the vagina and its secretions at the time of speculum examination. With this information most cases quickly sort out into one of the major categories listed in Table I. Without these procedures, diagnosis becomes guesswork.

Candida

Women with *Candida* infection usually complain of itching and a three-dimensional discharge is seen adherent to an inflamed mucosa. The pH is almost always acidic, allowing the Nitrazine paper to remain a yellowish color (4.0 to 5.0). Clumps of branched and budding hyphae can be found on the wet smears. However, the organisms often are not obvious and many fields must be carefully scanned before finding a single typical organism.

Candida albicans accounts for most candidal infections, but about 10% are due to *C.* (formerly *Torulopsis*) *glabrata.*[3] In *C. glabrata* species infections, no filaments are seen. Instead, there are only clusters of ovoid to round spores. These have a homogeneous ground-glass appearance with birefringent borders but lack the dimpling and pink tinge seen in red cells.[4] Clinically, *C. glabrata* infections are initially seen with burning rather than itching, there is little discharge, and only moderate erythema is noted. *C. glabrata* infections are comparatively resistant to the imidazole compounds in vivo, and require higher concentrations of the drug to inhibit their growth in vitro.[5-7]

In all cases of *Candida* vaginitis, of both *C. albicans* and *C. glabrata* types, in the absence of known allergy, a 1% aqueous solution of gentian violet will provide the most immediate and effective relief. Both *C. albicans* and *C. glabrata* are exquisitely sensitive to this agent. When properly applied, it is not objectionably "messy," and its routine use *at the time of diagnosis* will render any other therapy that much more effective. With the speculum in place and open, all visible discharge is swabbed out with use of the large rectal-type swabs now commonly available. Next a fresh swab soaked in the dye solution (but not dripping) is used to "paint" the cervix and all fornices as well as the exposed lateral walls seen between the open speculum blades. The speculum is then rotated 45 degrees, and previously covered mucosa is exposed and painted anteriorly and posteriorly all the way to the introitus. Rotation of 90 degrees in the opposite direction will reveal additional areas that require the same procedure. Only then may the speculum be slowly closed and withdrawn. If excess dye has been used, the liquid will form a visible pool on the mucosa as the speculum is removed. In this case, before closing the blades, insert a dry swab to absorb this excess so that it will not run out and cause external staining. The introitus, of course, should be painted along with the perianal area but never with a quantity sufficient to stain other areas of uninvolved skin. The end result should be a uniform coating of the entire vaginal epithelial surface with the fungicidal solution. The patient is given a minipad or liner to wear home "just in case," but patient complaints are almost nonexistent when this protocol is followed. Other forms of gentian violet application (self-inserted pessaries, gels, or treated tampons) are not effective in my experience. Patients should, of course, be warned of the possibility of staining and should use inexpensive underwear or pantyliners for at least 72 hours. Coitus, of course, should be discouraged, and tampons are not helpful at this time. Clotrimazole suppositories may be used nightly for 1 or 2 weeks, after which time I ask the patient to return if there are any further symptoms. Sometimes a second treatment is needed, but this is not usual.

Recurrent or chronic *Candida* vaginitis is a more complex problem and requires additional testing and therapy.[8] Recurrent symptoms alone are not sufficient for diagnosis. The organism itself must be identified by wet smear or special fungus culture before one can be certain of recurrent disease, since other conditions may present in a similar fashion. Once the diagnosis is confirmed, however, a number of problems must be considered.

If diabetes mellitus is not known to be present, the subclinical form should be ruled out with fasting and postprandial blood sugar testing. A diabetic partner may have penile candidiasis and be a source of reinfection. Most candidal infections are autogenous, and the organisms are transferred from the anus after defecation. Incorrect hygiene habits (wiping back to front, overuse of laxatives or stool softeners) may contribute to the problem and are easy to correct once discovered. A 3-month course of oral nystatin (10,000 U) taken three times a day with meals will greatly diminish the gastrointestinal population of *Candida* and decrease the inoculum on the perineum available for reinfection.

Many patients can identify specific times when recurrences are most likely, which are sometimes related to menses or coitus. At those times the use of prophylactic clotrimazole inserts or creams or potassium sorbate suppositories (currently available as Summer's Eve suppositories) may be helpful.

The important role of diet in this disorder has recently been clarified.[9] Ingestion of excessive dairy products, sucrose, and artificial sweeteners leads to the excretion of urine sugars that promote *Candida* infections. Dietary control can lead to dramatic reduction in the frequency of recurrent disease. Failure to elicit a sufficiently detailed sexual history may result in missing the patient with recurrent *Candida* whose extent of oral-genital contact is significant. *Candida* can certainly be transmitted orally from or via the partner. The use of an antiseptic fungicidal mouthwash prior to contact is a good recommendation. Finally, every documented recurrent vaginal infection should be acutely treated at the time of diagnosis with 1% gentian violet applied under direct vision, followed by application of topical clotrimazole for 7 days.

A small group of patients will be unresponsive to all of the foregoing suggestions. This group should be evaluated for specific *Candida* immune deficiency. Some individuals, despite repetitive exposure to the fungus, fail to express cell-mediated immunity to *Candida* antigens when applied as a forearm skin test. Their skin reactions to other common antigens (mumps, streptokinase, purified protein derivative) are normal as are lymphocyte mitogen studies and immunoglobulin levels. The cause of this phenomenon is unknown, and there is no proven therapy.[10] However, it may be a temporary condition. College students during times of academic stress may lose skin reactivity to candidin and concomitantly develop candidal vaginitis. They frequently recover their immune reactions and reestablish their vaginal health once the stress subsides.

Gardnerella

Gardnerella vaginalis vaginitis (formerly known as *Haemophilus* or *Corynebacterium vaginale*) is the second most common variety of vaginal disease seen in this country. In some practices it is the most common of all, whereas others may see it more rarely. As a rule, it is sexually transmitted and caused by an organism named after Herman L. Gardner, the clinician-investigator who first described the clinical characteristics of the disease and the microbiologic criteria of the agent.[11]

Patients infected with *Gardnerella* note variable amounts of discharge, which is usually of thin consistency and may have an unpleasant odor. The malodor is often especially noticeable after coitus, when the alkaline seminal fluid has resulted in the release of volatile amines and fatty acids. Patients should be asked if they or their partners have noted this feature. To some it is "fishy" or "musty." It is not unlike the odor of stale air that escapes from an automobile tire on deflation. These substances are attributed to the anaerobic organisms *Bacteroides* and *Peptostreptococcus*, which are frequent concomitant pathogens in patients with *Gardnerella*.

The vaginal pH will measure between 5.0 and 6.0, turning Nitrazine paper a greenish shade. On speculum examination the mucosa does not appear particularly inflamed unless a mixed infection is present. Most laboratories can now identify the organism from a routine vaginal swab if specifically alerted to the possibility of its existence. But such confirmation is expensive and rarely necessary. The saline wet smear can be diagnostic, especially in the presence of corroborating clinical signs. Clue cells are mature, flat vaginal squames, alone or more frequently in clusters, whose surfaces are coated with adherent *Gardnerella* coccobacilli. This phenomenon results in a uniformly granular appearance that is easily recognized. Isolated clumps of nonadherent organisms may also be seen in the smear fluid. Unless an additional infection is also present, white cells are rarely a prominent component of the cellular picture.

After discussion of the diagnosis and probable route of infection, both the patient and her partner should be treated. I emphasize the "ping-pong" nature of these infections rather than dwell on or speculate as to their origin. Since incubation time can be variable, I believe it unwise and invalid to be too dogmatic, or worse, judgmental. Still, partner treatment needs appropriate emphasis and most patients seem to understand.

A variety of other effective treatment regimens are available for this disorder. The first-line drug of choice is metronidazole, 500 mg twice daily for 7 days. Shorter courses with higher dosages are not as effective.[16] When this drug cannot be used, ampicillin, 500 mg four times daily for 7 days, and amoxicillin, 500 mg four times daily for 7 days, are also effective; there is some evidence that in males these drugs may be more effective than metronidazole.[13] Cephradine, 500 mg four times daily for 7 days, should be tried in stubborn cases and may work when others fail. Drug allergies, pregnancy, and failure of prior therapy all influence individual choice. Adjunctive therapy, especially when anaerobes are present, as evidenced by presence or complaint of odor, consists of a nightly douche of hydrogen peroxide. The over-the-counter stock solution of 3% concentration is diluted with four parts of water and used as a retention douche. After one half of a pint of the solution has entered the vagina and expanded its walls, the lips are held tightly closed for as long as possible up to 3 minutes and the solution is allowed to escape. This process is then repeated and continued at bedtime for 1 week, during which time coitus without use of a condom is not allowed.

Trichomonas

The introduction of oral Flagyl has greatly decreased the incidence of this disease during my professional lifetime. However, *Trichomonas vaginalis* still accounts for about one fourth of the common cases of vaginitis. It is frequently seen in association with condylomata acuminata.

Classically the organism produces a copious discharge that may or may not be pruritic. However, the amount of discharge is dramatic and almost always is noted by the patient, who frequently feels "wet." There is a variable amount of erythema of the vaginal mucosa, but the characteristic "strawberry" appearance caused by intraepithelial microabscesses is rarely seen except during pregnancy. The pH is usually very alkaline, giving a dark green to deep purple reaction on Nitrizine paper. The saline solution smear is commonly loaded with white cells, most of which are recognizable as polymorphonuclear leukocytes. The only other condition that produces such a heavy white blood cell response is atrophic vaginitis and in that case, parabasal epithelial cells are usually seen as well. Therefore, with mature squames and copious white cells in a discharge with a pH between 6 and 7, the evidence for *Trichomonas* is overwhelming.[12] As a rule, the typical motile protozoa are also visible, but this is not always the case. Sometimes they are only recognizable by use of an ×40 objective and adjustment of the condensor for optimum contrast. Then, by carefully and slowly focusing up and down and concentrating at one pole of what you think may be a trichomonad, you may see propellor-like movement at the cell's surface indicating the presence of flagellae. But even when the organism itself cannot be seen, a diagnosis is warranted if the other characteristics are present.

Treatment, except in the first trimester of pregnancy or in cases of known allergy or chronic alcoholism, rests with use of oral metronidazole. A single 2 gm dose, divided into 1 gm in the morning and 1 gm at night, has been clinically effective and elicits good patient compliance with very few side effects. Unless the partner is treated in a similar fashion at the same time, condoms must be used to prevent reinfection. Studies have shown that the normal male may spontaneously clear an uncomplicated trichomonal infestation without specific therapy, but whenever a woman complains of recurrent disease, a cure cannot be achieved unless the partner(s) are also treated.

Nevertheless, in recurrent *Trichomonas* sexual reinfection is not the only source of disease. Unlike herpes, the trichomonad may survive in tap water, soap water, bubble baths, chlorinated swimming pools, and hot tubs.[14] These avenues of possible reinfection should be investigated before proceeding with higher doses of metronidazole. Some strains of the organism are in fact resistant to the drug, but most are only relatively so. Thus giving large doses over longer periods of time, for example, 1 gm twice daily for 7 days, helps many of these patients.

Adjunctive therapy is the use of clotrimazole vaginal cream or inserts. These are topical imidazoles from the same pharmaceutical family and act in a similar fashion. Hypertonic (20%) saline solution douches are also very effective. Their use in pregnancy, however, carries the theoretical danger of premature membrane rupture, should the saline solution contact the amnion.

Among the remaining 10% of women with complaints of vaginitis, a large number are mistakenly interpreting the presence of a discharge as evidence of infection. It is extremely important to identify these individuals, since they are in fact normal. Misguided attempts at "therapy" may instead destabilize their normal ecology and result in actual disease. The vagina normally sheds squamous cells at a predictable rate. These mix with cervical mucus and form a discharge that is white and opaque. Normally, this discharge is of negligible amount and causes no symptoms. In large quantities, however, it is easily mistaken for *Candida*. At times of stress and probably in response to other factors not yet understood, the rate of vaginal desquamation increases and the amount of discharge becomes alarming to the patient who must usually absorb it on a pad or tampon. Yet this is a "physiologic" event. The mucosa is pink, the pH is 4.0 to 5.0, and wet smears show mature squames, normal lactobacilli, an absence of white cells, and no spores or filaments. Such women should be told the truth about their discharge. Occasional cleansing douches with diluted vinegar or saline solution probably do no harm, but all other temptations to "treat" the condition generally only make it worse. In time, perhaps as the patient's life situation changes, the discharge decreases once again. These patients are seen with some frequency and must be distinguished from the very unusual patient with "psychosomatic" vaginitis.

Rarely, a patient will present with a long list of prior physicians and prior medications, all having failed to produce a cure for her incapacitating vaginitis, which characteristically prevents coitus. The routine diagnostic procedures elicit no pathologic findings: the cells, flora, pH, and mucosa are normal. A history of presumed "allergy" to all known vaginal therapy, and a demonstrable degree of emotional liability help to confirm the impression of a functional disorder.[15] Such patients are best referred for psychiatric evaluation and assistance, but most are extremely reluctant to accept this suggestion. Nevertheless, nothing else has seemed to help such patients.

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Preventing febrile complications of suction curettage abortion

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To identify risk factors for febrile complications after suction curettage abortion, we analyzed the data of 26,332 women who underwent suction curettage abortion at five participating centers in the Joint Program for the Study of Abortion, Part III, from 1975 to 1978. We defined febrile morbidity as an oral temperature of ≥38° C for 2 days or longer. The febrile morbidity rate was 0.34 per 100 abortions. We performed a multivariate analysis using a linear logistic regression model. Prophylactic antibiotics proved to be the most protective factor, reducing the rate of febrile complications to about one third that of women who received no prophylactic antibiotics (relative risk 0.36; 95% confidence interval 0.18 to 0.70). Patients who had had one or more previous births also had a significantly lower risk of febrile morbidity (relative risk 0.54; 95% confidence interval 0.33 to 0.88). Other factors did not significantly affect the febrile complication rate. (AM J OBSTET GYNECOL 1985;152:252-5.)

Key words: Abortion, complications, infection, prophylactic antibiotics

Infection is one of the most common and most serious complications of suction curettage abortion. Although reported febrile complication rates associated with suction curettage are relatively low, determining the factors associated with febrile complications is important because (1) abortion is so commonly performed that even small reductions in morbidity would have important public health impact and (2) infection is the most common cause of deaths from legal abortion.[1] Despite the clinical and public health importance of infection, the risk factors for postabortal infection are not well understood.

Several risk factors for postabortal infection have been identified. The type of anesthesia,[2] method of dilation,[3] and physician skill[4] have been reported to influence postabortion morbidity. In one institution, however, physician experience, as expressed by the number of procedures performed, was not related to the complication rate for procedures performed by that physician.[5] Untreated endocervical gonorrhea has been found to triple the risk of endometritis after abortion.[6] Finally, one study has suggested that nulliparous women undergoing abortion have a higher risk of complications after abortion than do multiparous women.[7]

This study was designed to document the incidence of febrile complications after suction curettage, to identify risk factors, and to recommend ways of preventing febrile complications.

Material and methods

The Joint Program for the Study of Abortion, Part III, is a multicenter, prospective study of legal abortion complications. This study was conducted by the Centers for Disease Control during the period 1975 to 1978. Part III is a continuation of the Part I investigation conducted by the Population Council, from 1970 to 1971, and the Part II study conducted by the Centers for Disease Control from 1971 to 1975. Participants in Part III included university hospitals and proprietary hospitals and clinics. Of the 13 study contractors, nine were hospitals and four were clinics. The four clinics, however, provided 54% of the case reports. In each participating institution, trained abstractors transcribed information from patient's charts to standardized forms.

We defined febrile morbidity as an oral temperature of ≥38° C on 2 or more days. Gestational age was defined as the difference between the date of abortion and the date of the last menstrual period, unless one or both dates were unknown or the calculated gesta-

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tional age differed by more than 2 weeks from the physician's estimate. In those instances, the physician's estimate of gestational age was used.

The distribution of use of prophylactic antibiotics varied greatly between the different participating institutions. Since we needed to control for institution in our analysis, we analyzed data only from the institutions that performed abortions both with and without prophylactic antibiotics. Five institutions met this criterion. We also excluded women having concurrent tubal sterilization, ectopic pregnancy, or hydatidiform mole. In total, we studied 26,332 women who underwent suction curettage abortion at 12 weeks' gestation or earlier.

We first calculated the crude relative risk of febrile complications for all major variables. These included age, number of previous pregnancies, number of previous deliveries, number of spontaneous abortions and stillbirths, number of previous induced abortions, marital status, ethnic group, weeks of gestation, type of abortion procedure, type of suction cannula, type of dilators, size of suction cannula, type of anesthesia, use of prophylactic antibiotics, preexisting medical condition, and the insertion of an intrauterine contraceptive device after abortion.

We then performed multivariate analyses, using a linear logistic regression model.[8] By using this model, we controlled simultaneously for potential confounding factors in order to produce adjusted relative risk estimates. Certain variables, however, such as the use of laminaria, occurred too infrequently to analyze as part of the multivariate model.

We used the method of Kleinbaum et al.[9] to assess confounding and effect modification. We observed no statistically or clinically significant interactions among the factors we assessed, but substantial confounding was present in our data. To examine the independent effects of risk factors on febrile complications and to control for confounding, we examined the following six factors in the linear logistic regression model: type of suction cannula, use of prophylactic antibiotics, level of physician training, type of anesthesia, previous delivery, and institution where the abortion was performed. All six factors had to be known before a woman could be included in the multivariate analysis. In total, the requisite information was known for 24,831 of the 26,332 women. Of the 90 febrile complications, 84 were included in the model. Finally, we examined the impact of number of previous deliveries on the incidence of retained products of conception and recurettage as treatment of a complication.

Results

Characteristics of women in the study were similar to those of women in the United States who obtained abortions during these years.[10] Thirty percent of all women in this study were 19 years of age or younger (Table I). The race of 27% of patients was not reported because some facilities did not record this information. Most women (59%) had had no previous delivery. About 80% of the abortions were performed within 10 weeks of the last menstrual period.

Table I. Patients with suction curettage abortions, by selected characteristics

Characteristic	*No.*	*%*
Age (yr)		
≤19	7998	30.4
20-24	8160	31.0
25-29	6437	24.5
30-34	2316	8.8
≥35	1371	5.2
Unknown	50	0.2
Ethnic group		
White	10,300	39.1
Black	4689	17.8
Others	4226	16.0
Unknown	7117	27.0
Previous delivery		
0	15,393	58.5
≥1	10,838	41.2
Unknown	101	0.4
Weeks of gestation		
≤8	10,728	40.7
9-10	10,354	39.3
11-12	5250	19.9
Total	26,332	100.0

Ninety cases of febrile morbidity were reported among 26,332 suction curettage abortions, for a rate of 0.34 per 100 abortions. Women who received prophylactic antibiotics and women who had had previous deliveries were less likely to have febrile complications than other women (Table II). Prophylactic antibiotics given at the time of abortion offered the most protection, reducing the rate of febrile complications to one third that of women who received no prophylactic antibiotics. As compared with women who had not given birth, women who had had one or more previous births had about one half the risk of febrile complications.

The other factors examined did not significantly affect the febrile complication rate (Table II). Use of general anesthesia was associated with lower rates of febrile complications (relative risk 0.80) compared to use of local anesthesia, but this difference was not statistically significant. Resident physicians were associated with higher rates of febrile complications (relative risk 1.3) compared to attending physicians, but this difference was not statistically significant. Finally, use of a rigid cannula was associated with higher rates of febrile complications (relative risk 1.6) compared to use of a flexible cannula, but again this difference was not significant.

Women who had had no previous deliveries had lower rates of both retained products of conception and

Table II. Adjusted relative risks of a febrile complication*

Factor	*Adjusted relative risk estimate*	*Relative risk association*
Prophylactic antibiotics	0.36 (0.18-0.70†)	Prophylaxis vs. no prophylaxis
Previous deliveries	0.54 (0.33-0.88)	Previous delivery vs. no previous delivery
Type of anesthesia	0.80 (0.33-2.0)	General vs. local anesthesia
Level of physician training	1.3 (0.77-2.3)	Resident vs. attending physician
Type of suction cannula	1.6 (0.70-3.6)	Rigid vs. flexible cannula

*Results from a multivariate linear logistic regression model on 24,831 women with all the factors listed in this table being in the model as well as individual institution.

†Numbers in parentheses are 95% confidence intervals.

recurettage as treatment of a complication. The rate of retained products of conception was 0.54 per 100 abortions for women with no prior deliveries, in contrast to 0.78 for women with one or more deliveries (relative risk 0.7; 95% confidence interval 0.5 to 0.9). Similarly, the rate of recurettage was 0.67 per 100 abortions for women with no prior deliveries, in contrast to 0.93 for those with one or more deliveries (relative risk 0.7; 95% confidence interval 0.6 to 0.9).

Comment

The rate of febrile morbidity associated with suction curettage in this study (0.34 per 100 abortions) lies within the reported range of 0.1 to 6.0 per 100 abortions.[7, 11, 12] The wide range in reported rates reflects both different case definitions of "febrile morbidity" and different years included in various study periods. Because of the lack of uniform definitions and diagnostic criteria, rates of infectious complications including endometritis, salpingitis, or peritonitis are difficult to interpret. Fever can provide a more objective estimate of the incidence of infectious morbidity,[1] yet it is not an ideal indicator of infection.[2]

In this study two factors emerged as important in reducing the likelihood of febrile complications of suction curettage; the first can be influenced by the physician, while the second cannot. Six reports, including both randomized clinical trials and cohort studies,[13] have examined the efficacy of prophylactic antibiotics for suction curettage. All studies have shown a protective effort. In this study women who received prophylactic antibiotics (usually tetracycline) had a significantly lower risk of febrile morbidity than women who did not receive antibiotics.

This report is the seventh, of which we are aware, to demonstrate that use of prophylactic antibiotics reduces the risk of infection after curettage abortion. To place this observation in clinical perspective, two concerns need to be addressed. (1) Given the low incidence of infection in this setting, is the benefit of prophylaxis worth the cost? (2) Are there alternatives to routine prophylaxis? We recently estimated that the cost of routine prophylaxis with an expensive tetracycline (doxycycline) would be offset by the savings resulting from the reduction in short-term morbidity alone.[13] In this model, however, we did not take into account the sizable human and economic costs of ectopic pregnancy and infertility, which may be associated with upper genital tract infection.

Two alternatives to routine prophylaxis deserve consideration. One is providing prophylaxis only to those women identified by history to be at high risk of infection, and the other is obtaining cervical cultures for organisms such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* several days before abortion and treating women with positive cultures before abortion. At present, factors in a woman's medical history that might serve as indicators of risk are too unreliable to be clinically useful. The second strategy would add delays, cost, and inconvenience for all women seeking curettage abortion and hence does not appear practical.[13]

Women who had had one or more previous deliveries had about half the risk of febrile morbidity as women without such a history. The explanation for this protective effect is unclear. Cervical dilation and subsequent uterine evacuation may be easier to perform in parous women, whose cervices may be more compliant.[14] However, the higher rates for both retained products of conception and recurettage as treatment among parous women do not support this hypothesis.

Little information has been published on the effect of parity on abortion complications. In the first phase of the Joint Program for the Study of Abortion,[12] total complication rates showed no consistent pattern by parity. In another study,[7] women who had had their first pregnancy aborted had a slightly higher rate of total complication than did those who obtained abortion after one or more live births.

The second phase of the Joint Program for the Study of Abortion[15] found that use of local anesthesia was associated with a significantly increased risk of febrile complications. It was postulated that less thorough curettage might have accounted for this observation. When a woman is conscious during an abortion, the physician may dilate the cervix to a smaller diameter and take less time for curettage than he would if the patient were unconscious. Although our analysis also found use of local anesthesia to be associated with a higher risk of febrile morbidity, this difference was not statistically significant.

In conclusion, administration of prophylactic antibiotics appears to be the best way to reduce the risk of febrile morbidity from suction curettage abortion. In addition, nulliparous women appear to be at increased risk of this complication. Thus, prophylactic antibiotics may be especially beneficial for nulliparous women undergoing suction curettage abortion.

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The relationship between perinatal hypoxia and newborn encephalopathy

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Newborn encephalopathy was observed in 30% of 303 selected high-risk preterm and term newborn infants. The newborn encephalopathy was mild or moderate in 65 children and severe in 27. The predictive significance of newborn encephalopathy to motor and cognitive deficits at 1 year was evident from the incidence of deficits in the children with no encephalopathy (17%), in children with mild or moderate encephalopathy (25%), and in children with severe encephalopathy (55%). The biologic risk factors with a significant association with newborn encephalopathy included severe intrapartum fetal hypoxia, moderate and severe newborn respiratory complications, and major infections. Perinatal hypoxia was associated with, and may have contributed to, 26% of the cases of mild and moderate newborn encephalopathy and 66% of the cases of severe newborn encephalopathy. Fetal and newborn hypoxia occurred with equal frequencies in cases of mild and moderate encephalopathy; however, newborn hypoxia was twice as frequent as fetal hypoxia in cases of severe newborn encephalopathy. (AM J OBSTET GYNECOL 1985;152:256-60.)

Key words: Newborn encephalopathy, fetal and newborn hypoxia, infection

Newborn encephalopathy represents the neurological manifestations of newborn central nervous system disorders. Newborn encephalopathy, particularly with seizures and recurrent apnea, has been demonstrated to be an important predictor of subsequent motor and cognitive handicap.[1, 2]

The importance of perinatal hypoxia accounting for newborn encephalopathy has been implied by a number of studies. Clinical studies of birth asphyxia with severe newborn depression have demonstrated that most children who survived with sequelae had clinical signs of encephalopathy during the neonatal period.[3] Similarly, studies of children mature at birth with clinical markers of intrapartum hypoxia and hypoxic ischemic encephalopathy have demonstrated subsequent deficits in 25% to 50% of surviving children.[4] The objective of the present study was to provide further evidence of the relationship between fetal and newborn hypoxia and the spectrum of newborn encephalopathy as observed in selected high-risk preterm and term newborn infants.

Methods

Included in this study were 303 high-risk children, of whom 152 were premature and 151 were mature at birth. The high-risk children selected had one or more of the following fetal-newborn complications: very low birth weight (<1500 gm), fetal growth retardation, a diabetic mother, moderate or severe newborn respiratory complications, major newborn infection, or newborn encephalopathy. A prospectively documented perinatal database, with particular attention to the presence or absence of encephalopathy in the newborn period, was obtained. Subsequently, a follow-up assessment was carried out to 12 months of age to evaluate the motor and cognitive development of each child.

The perinatal database included maternal characteristics, maternal medical and obstetric complications, labor and delivery characteristics, newborn characteristics, and complications during the neonatal period. Maternal characteristics included age, weight, gain in weight during pregnancy, and height. Maternal medical complications included cardiopulmonary disease, hypertension, renal disease, and diabetes. Obstetric complications included previous pregnancy wastage, antepartum hemorrhage, toxemia, premature rupture of membranes, and premature labor and its management. Labor characteristics, analgesia and anesthesia, and mode of delivery were documented. Socioeconomic status was established by an in-hospital interview, and the Caldwell Home Observation for the Measurement of the Environment Scale was completed in the home when the infant was 6 months of age.

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The fetal and newborn risk factors included: (1) fetal maturity at delivery as expressed by gestational age and birth weight; (2) fetal growth retardation (excluding major anomalies) in which birth weight was less than the third percentile for gestational age; (3) anomalies (excluding genetically determined and central nervous system anomalies); (4) insulin-dependent diabetic mothers; (5) intrapartum fetal hypoxia defined by an umbilical artery buffer base <34.0 mmol/L; (6) newborn respiratory complications classified as mild if requiring oxygen therapy only, moderate if requiring continuous positive airway pressure, and severe if requiring mechanical ventilation; (7) newborn infection classified as either minor (e.g., conjunctivitis) or major (e.g., septicemia meningitis); (8) newborn hypoglycemia defined by a blood glucose <20 mg/100 ml in preterm and <30 mg/100 ml in term infants.

The diagnosis of encephalopathy was based upon the continuous observations of the physicians and nursing staff of the Neonatal Intensive Care Unit. The criteria upon which the diagnosis was based included behavioral changes, abnormalities of tone, seizures, and recurrent apnea. The abnormalities of behavior, irritability, jitteriness, lethargy, and coma were identified by observations of spontaneous movement of the newborn infant. Increased and decreased tone was identified during observations of posture and active or passive movement. Seizures observed included subtle, tonic, and clonic ones, as described by Volpe.[5] Recurrent apnea, a repetitive respiratory pause greater than 20 seconds requiring active resuscitation was identified as a manifestation of newborn encephalopathy when out of keeping with associated respiratory complications. Newborn encephalopathy was classified as mild, moderate, or severe according to the criteria outlined in Table I.

Follow-up assessments were carried out at 6 and 12 months of age, corrected for the preterm children. Motor and cognitive assessment included a neurological examination, and use of the Bayley Scales of Infant Development, from which a Physical Development Index and Mental Development Index was derived, and an Uzgiris and Hunt Scale. The multiple serial outcome measures in most of the children provided complementary observations that reinforced particularly the interpretation of minor motor and cognitive deficits. Each child was classified either as "normal" or as having a major or minor deficit of motor and/or cognitive development according to criteria previously established.[6]

Statistical analysis to investigate the relationship between perinatal risk factors and encephalopathy in the newborn period and motor and cognitive deficits at 1 year included cross-tabulation and χ^2 analysis. Stepwise logistic regression analysis was used to examine the multivariate associations of fetal and newborn risk factors with newborn encephalopathy.

Table I. Classification criteria for mild, moderate, and severe newborn encephalopathy

	Newborn encephalopathy		
	Mild	*Moderate*	*Severe*
Behavior	Hyperalertness Irritability Jitteriness	Lethargy	Coma
Tone	Transient hypertonia and hypotonia	Severe hypotonia	
Seizures		Occasional	Multiple
Respiration			Recurrent apnea

Results

The frequency of newborn encephalopathy and the incidence of deficits at 1 year of age are outlined in Table II. The increased incidence of motor and cognitive deficits in children with newborn encephalopathy, particularly when severe, was evident in both preterm and term children ($p < 0.001$). Sixty-five children had mild-moderate encephalopathy, of whom 20 had behavioral changes only, whereas 45 exhibited abnormalities of tone with or without behavioral changes. Twenty-seven children were classified as having severe encephalopathy because of seizures and/or recurrent apnea (Table III). Multiple seizures were observed in 14 children, 10 of whom were mature at birth; and recurrent apnea was observed in 20 children, 14 of whom were premature at birth.

The relationship between each perinatal factor and newborn encephalopathy was analyzed. No significant relationships were identified between newborn encephalopathy and the socioeconomic status, maternal medical and obstetric complications, and labor and delivery characteristics documented in this study. The fetal and newborn biologic risk factors studied included gestational age, birth weight, growth retardation, diabetic mothers, selected anomalies, fetal hypoxia, newborn respiratory complications, newborn infections, and newborn hypoglycemia. Significant relationships to newborn encephalopathy were demonstrated by fetal hypoxia when the umbilical artery buffer base was less than 30 mmol/L, by newborn respiratory complications when moderate or severe, and by major newborn infections (Table IV). The independent significance of each of these biologic risk factors with severe newborn encephalopathy was confirmed by means of a stepwise logistic regression analysis (Table V).

Table II. Frequency of newborn encephalopathy and proportion with motor or cognitive deficits at 1 year in selected high-risk preterm and term infants

	Total population					*Preterm*					*Term*				
	Total No.	*Normal*		*Deficits*		*Total No.*	*Normal*		*Deficits*		*Total No.*	*Normal*		*Defitis*	
		No.	*%*	*No.*	*%*		*No.*	*%*	*No.*	*%*		*No.*	*%*	*No.*	*%*
None	211	176	88	35	17	102	82	80	20	20	109	94	86	15	14
Mild-moderate	65	49	75	16	25	35	27	76	8	24	30	22	73	8	27
Severe	27	12	45	15	55	15	6	40	9	60	12	6	50	6	50

Table III. Manifestations of severe newborn encephalopathy in selected high-risk preterm and term infants with and without motor or cognitive deficits at 1 year

Manifestations of severe newborn encephalopathy	*Preterm*		*Term*	
	Normal (N = 6)	*Deficits (N = 9)*	*Normal (N = 6)*	*Deficits (N = 6)*
Multiple seizures	0	1	4	2
Recurrent apnea	5	6	2	0
Seizures and apnea	1	2	0	4

Table IV. Fetal-newborn biologic risk factors with a significant relationship to newborn encephalopathy

Biologic risk factors	*Total No.*	*Newborn encephalopathy*						*p Value*
		None		*Mild-Moderate*		*Severe*		
		No.	*%*	*No.*	*%*	*No.*	*%*	
Fetal hypoxia								
Umbilical artery buffer base								
≥ 30 mmol	278	200	72	57	20	21	8	< 0.01
<30 mmol	25	11	44	8	32	6	24	
Respiratory complications								
None—Mild	245	174	71	56	23	15	6	< 0.001
Moderate—Severe	58	37	64	9	15	12	21	
Newborn infection								
None—Minor	291	207	71	63	22	21	7	< 0.001
Major—Central nervous system	12	4	33	2	17	6	50	

Table V. Stepwise logistic regression analysis between the relevant biologic risk factors and severe newborn encephalopathy

Variable	χ^2	*Probability*
Intercept	97.2	
Newborn infection	12.6	< 0.001
Fetal hypoxia	7.9	< 0.01
Respiratory complication	7.6	< 0.01

A review was made of the proportion of the children with mild-moderate or severe newborn encephalopathy with one or more of these significant fetal newborn risk factors. Risk factors were observed in 18 children with mild-moderate encephalopathy and in 17 children with severe encephalopathy. Newborn respiratory complications occurred most frequently, in 14% of the children with mild-moderate and in 44% of those with severe encephalopathy. Fetal hypoxia occurred in 12% of those with mild-moderate and in 22% of those with severe encephalopathy. Major newborn infections occurred in 3% of those with mild-moderate and in 22% of those with severe encephalopathy.

Comment

Observations of encephalopathy as a marker of central nervous system insult are an essential part of the assessment of newborn infants. The identification of encephalopathy is as important in the preterm as in the term newborn infant. However, this identification can be complicated because of the ventilation and concurrent medication required, particularly by the very low–birth weight infant. Seizures, which are more common in term newborn infants, were observed in preterm

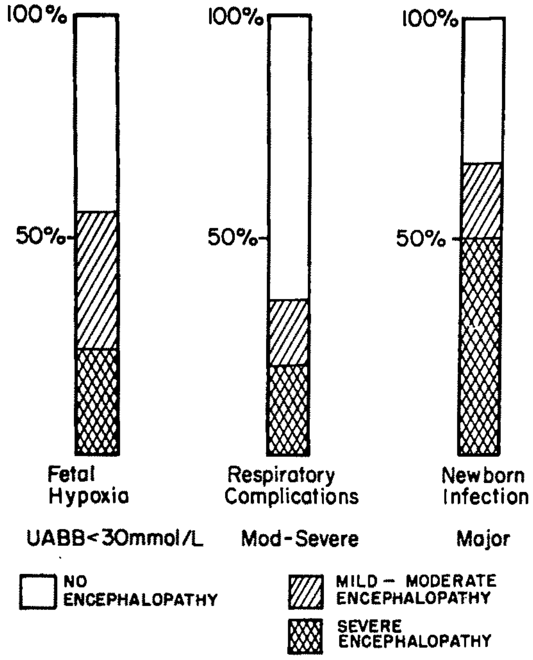
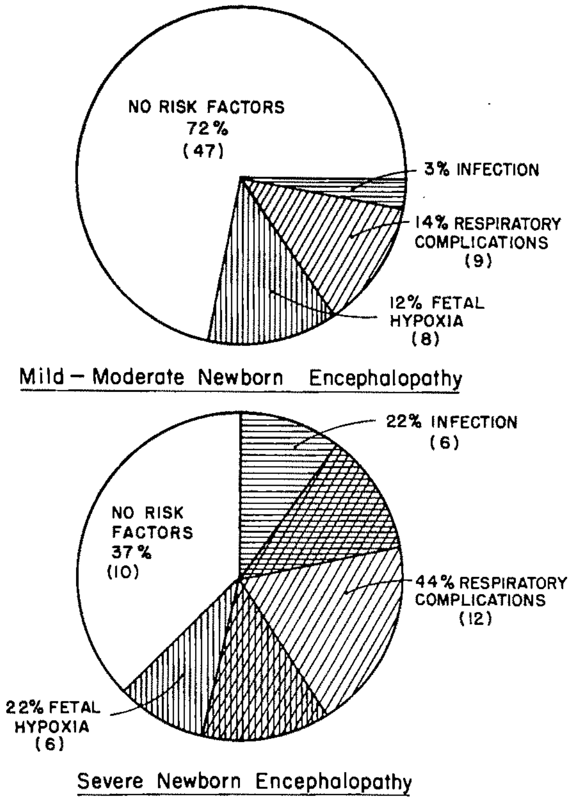


Fig. 1. Incidence of newborn encephalopathy in children with significant fetal hypoxia, moderate and severe respiratory complications, and major newborn infections. *UABB*, Umbilical artery buffer base.



Mild – Moderate Newborn Encephalopathy

Severe Newborn Encephalopathy

Fig. 2. Incidence of significant biologic risk factors observed in the high-risk children with mild-moderate encephalopathy and severe encephalopathy.

infants. This study, in keeping with previous reports,[5,7] emphasizes the importance of recurrent apnea as an indication of severe newborn encephalopathy.

The incidence of newborn encephalopathy depends on the population of children studied and the criteria used to define newborn encephalopathy. In this study, the incidence of preterm and term children at risk because of fetal-newborn complications was 30%; of these, 21% were classified as having mild-moderate encephalopathy and 9%, severe encephalopathy.

The identification of newborn encephalopathy is important because of the predictive significance of this observation for future motor and cognitive deficits, particularly if the newborn encephalopathy is severe. This has been well documented in previous studies, although the frequency of deficits has varied somewhat with the populations studied and the outcome criteria used in the follow-up studies to identify motor and cognitive deficits. The incidence of deficits in children with a presumptive diagnosis of hypoxic-ischemic encephalopathy ranged from 21% to 56%.[8-10] Studies of children with seizures in the newborn period have reported an incidence of deficits that ranged from 20% to 49%.[11-13] The frequency of deficits in the present study—17% in children with no encephalopathy, 25% in children with mild-moderate encephalopathy, and 55% in children with severe encephalopathy—is, in general, in keeping with these reports.

Newborn encephalopathy has commonly been attributed to hypoxia and/or intracranial hemorrhage but may also occur with infection, metabolic disorders, and developmental disorders. The fetal-newborn risk factors in this study which demonstrated an independent significant relationship with severe newborn encephalopathy included severe intrapartum fetal hypoxia with an umbilical artery buffer base <30 mmol/L at delivery, moderate and severe newborn respiratory complications, and major newborn infections. The incidence of encephalopathy in children with these risk factors is summarized in Fig. 1. Newborn encephalopathy was observed in 56% of the children with severe fetal hypoxia, 36% of the children with moderate and severe respiratory complications, and 67% of the children with a major newborn infection. No association was observed between newborn encephalopathy and newborn hypoglycemia and the selected anomalies included in this study.

Hypoxia has been perceived to be an important mechanism that contributes to newborn encephalopathy. Studies of children with neonatal seizures have suggested that hypoxia may have been an etiologic factor in 48% to 65% of the children.[11,14] Volpe,[15] in a report on 100 consecutive mature children with hypoxic-ischemic encephalopathy, attributed 90% of the cases to definite or probable intrauterine fetal asphyxia and 10% to postnatal asphyxia due to severe pulmonary disease, recurrent apneic spells, or congenital heart disease. This suggests that, at least in mature children, fetal hypoxia is of greater importance than newborn hypoxia.

Current understanding of the relationship of intrapartum fetal hypoxia to newborn encephalopathy has been based, in large part, upon a demonstrated association between a presumptive diagnosis of hypoxia and encephalopathy. The presumptive criteria have included fetal distress during labor, including meconium, fetal bradycardia or decelerations, or birth asphyxia expressed by low Apgar scores at 1 and 5 minutes, and delayed onset of spontaneous respiration requiring positive pressure resuscitation. The present study endeavored to contribute to our understanding of this relationship by providing a definitive diagnosis of fetal hypoxia by means of an acid-base assessment with definition of a significant metabolic acidosis at delivery, an umbilical artery buffer base <30 mmol/L. On the basis of this criterion in these selected high-risk preterm and term children, intrapartum fetal hypoxia was associated with, and may have contributed to, 12% of the cases of mild-moderate encephalopathy and 22% of the cases of severe encephalopathy.

There was a significant association between moderate and severe newborn respiratory complications and newborn encephalopathy. The occurrence of hypoxic episodes in children with moderate and severe respiratory complications has been demonstrated with continuous transcutaneous oxygen electrode studies[16] which suggest that newborn hypoxia with or without ischemia may be a mechanism that accounts for central nervous system injury in respiratory complications. On the basis of these assumptions, newborn respiratory complications with hypoxia was associated with and may have contributed to 14% of the cases of mild-moderate encephalopathy and 44% of the cases of severe encephalopathy. The contribution of newborn hypoxia is, in large part, in the preterm children.

Although newborn infections are uncommon, approximately two thirds are associated with newborn encephalopathy, and in the present study infection was associated with and may have contributed to 3% of the mild-moderate cases and 22% of the severe cases of newborn encephalopathy.

The association of the significant biologic risk factors with newborn encephalopathy, and their possible contribution to it, is summarized in Fig. 2. Many other unidentified factors must have accounted for mild-moderate newborn encephalopathy, with no risk factors in 47 (72%) of the children. On the other hand, fetal-newborn hypoxia may have contributed to mild-moderate encephalopathy in 26% of the children, with approximately equal contributions of fetal and newborn hypoxia. These risk factors appeared to have played a much greater role in severe encephalopathy, with only 10 (37%) of the children having no risk factors. Fetal and newborn hypoxia may contribute to two thirds of the cases of severe encephalopathy, with newborn hypoxia twice as common as fetal hypoxia.

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Superficial laser vulvectomy

II. The anatomic and biophysical principles permitting accurate control over the depth of dermal destruction with the carbon dioxide laser

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The rationale for using the carbon dioxide laser to treat either vulvar intraepithelial neoplasia or extensive papillomaviral infections is to destroy the entire area of abnormal epithelium to a shallow depth, so that rapid healing will occur from normal keratinocytes in the underlying pilosebaceous glands. After the first laser impact, anatomic landmarks in the crater base are disguised by a layer of charred proteins, and any structure that is visible will already have suffered thermal necrosis. Accurate control of depth depends upon special surgical strategies that correlate the level of the underlying zone of thermal necrosis with specific visual appearances within the zone of vaporization. Maneuvers that limit depth of penetration to one of three desirable surgical planes (basement membrane, papillary dermis, midreticular dermis) are described. (AM J OBSTET GYNECOL 1985;152:261-71.)

Key words: Carbon dioxide laser, papillomaviral infection, vulvar intraepithelial neoplasia, accurate depth control

Lasers are devices that emit electromagnetic radiation in exactly the same spatial and temporal phase of the wave cycle.[1, 2] Such radiation is termed "coherent light." Because laser emissions are highly parallel and intensely monochromatic, these beams can be focused to an intensity that is many orders of magnitude greater than that attainable from conventional sources. The physical properties of the resulting emissions are a function of the medium used to produce that particular laser beam.

Electromagnetic radiation is generated when a previously excited quantum system (an atom, molecule, or ion) reverts back to a lower energy level. The type of interaction that will occur when this radiation impinges upon matter depends upon photon energy (that is, wavelength).[2] Absorption of high-energy photons (gamma rays, x-rays, and ultraviolet light) excites the orbiting electrons of the component atoms, resulting in ionization and consequent dissolution of molecular bonds. At the other end of the electromagnetic spectrum, radiation of increasingly longer wavelengths functions as electricity, sound, or radio waves. Photons from the middle of the spectrum (visible light, infrared, and microwaves) have insufficient energy to induce ionization but a wavelenth that is too short for use in telecommunication. Absorption of photons from this portion of the spectrum causes an increase in molecular vibration (heat). Since all currently used surgical lasers have wavelengths within the visible or infrared bands, their bioeffects are principally thermal. The type of wound produced by a particular laser emission is primarily determined by its extinction length in tissue (the slab thickness needed to absorb 90% of the transmitted radiation).[2]

The carbon dioxide laser emits intense coherent light in the far infrared region, with an extremely short extinction length (0.03 mm). Energy absorption at the impact site is very intense, resulting in (1) flash boiling of intracellular and extracellular water and (2) heating of anhydrous molecules (mainly proteins and nucleic acids) to incandescence. Flash boiling results in steam formation, leading to explosive disruption of tissue at the impact site. The net outcome is a surgical incision.[1] This zone of vaporization is surrounded by a narrow, charred zone of thermal necrosis. Surrounding that is another zone of sublethal thermal injury[2] (Fig. 1).

From the surgical viewpoint, there are two distinct types of bioeffects: (1) *the photophysical effect,* which is the immediate disruption of tissue, and (2) *the host effect,* which is a delayed effect due to the host inflammatory response in nondisrupted tissues.[1] Surgical control over the carbon dioxide laser beam depends upon a visual estimate of the extent of the immediate photophysical effects on the tissues being treated. However, any an-

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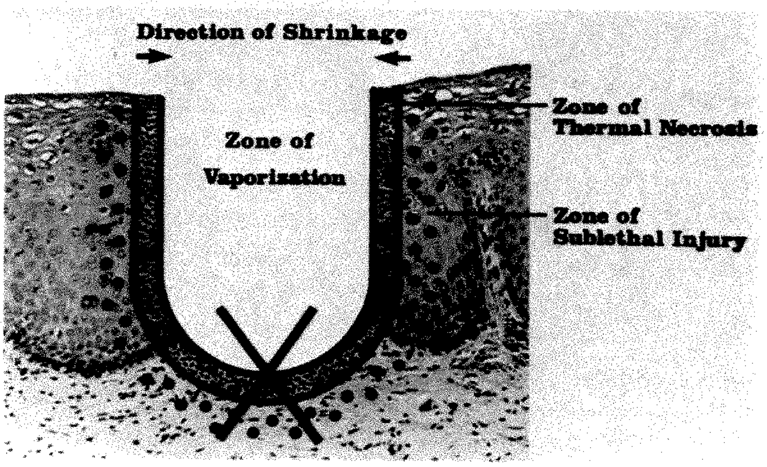

Fig. 1. Diagram of events at the laser impact site. The two major photophysical effects are tissue vaporization (due to flash boiling of intracellular and extracellular water) and tissue shrinkage toward the site of impact (due to desiccation at the crater margins). The zone of vaporization is surrounded by sharply defined zones of thermal necrosis and sublethal injury. Although these latter zones are immediately discernible in tissue sections, their clinical definition depends upon subsequent host response. Hence, any landmark visible in the crater base will have already suffered irreversible damage. The relationship between actual and desired depth of penetration shown in this diagram explains why optimum results elude so many laser surgeons.

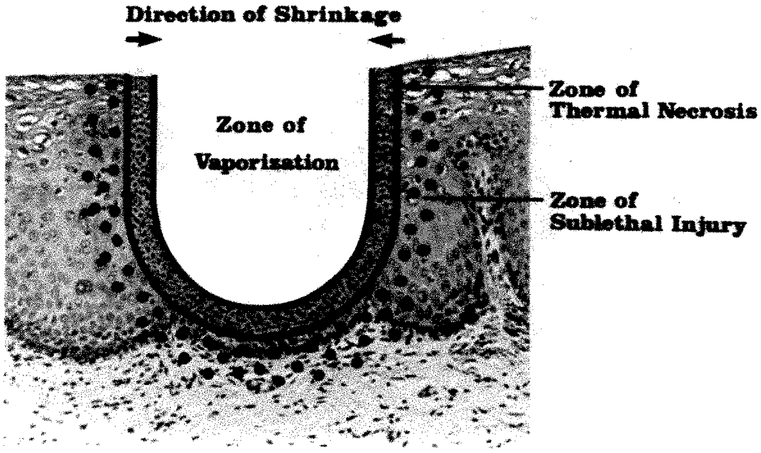

Fig. 2. The art of skilled laser surgery is to situate the zone of thermal necrosis (rather than the floor of the crater) at the desired depth.

atomic landmark that is visible in the base of the crater has already suffered irreversible thermal coagulation, and will be sloughed off over the succeeding week. Hence, the art of expert carbon dioxide laser surgery is to judge the depth of penetration so that the deepest margin of the zone of thermal necrosis corresponds to the desired depth of penetration (Fig. 2). Such techniques are quite feasible, but require the use of special surgical strategies.[3] This article describes an anatomically based method for precise control over the depth of dermal penetration during carbon dioxide laser surgery.

Human papillomaviruses are small, oncogenic DNA viruses that are now widely implicated in the etiology of cervical cancer.[4] Cellular nucleic acids extracted from both invasive and intraepithelial vulvar neoplasia contain the same papillomaviral types.[5] Sexually transmitted human papillomaviral infections in the female generally involve the entire anogenital squamous epithelium[6] and produce clinically obvious condylomas on the vulva and diffuse, nonpapillary epithelial hyperplasia on the cervix.

The rationale for using the carbon dioxide laser to treat either vulvar intraepithelial neoplasia or extensive papillomaviral infections is to destroy the entire area of abnormal epithelium to a shallow depth, so that rapid healing will occur from the keratinocytes in the underlying pilosebaceous glands.[7] Provided that destruc-

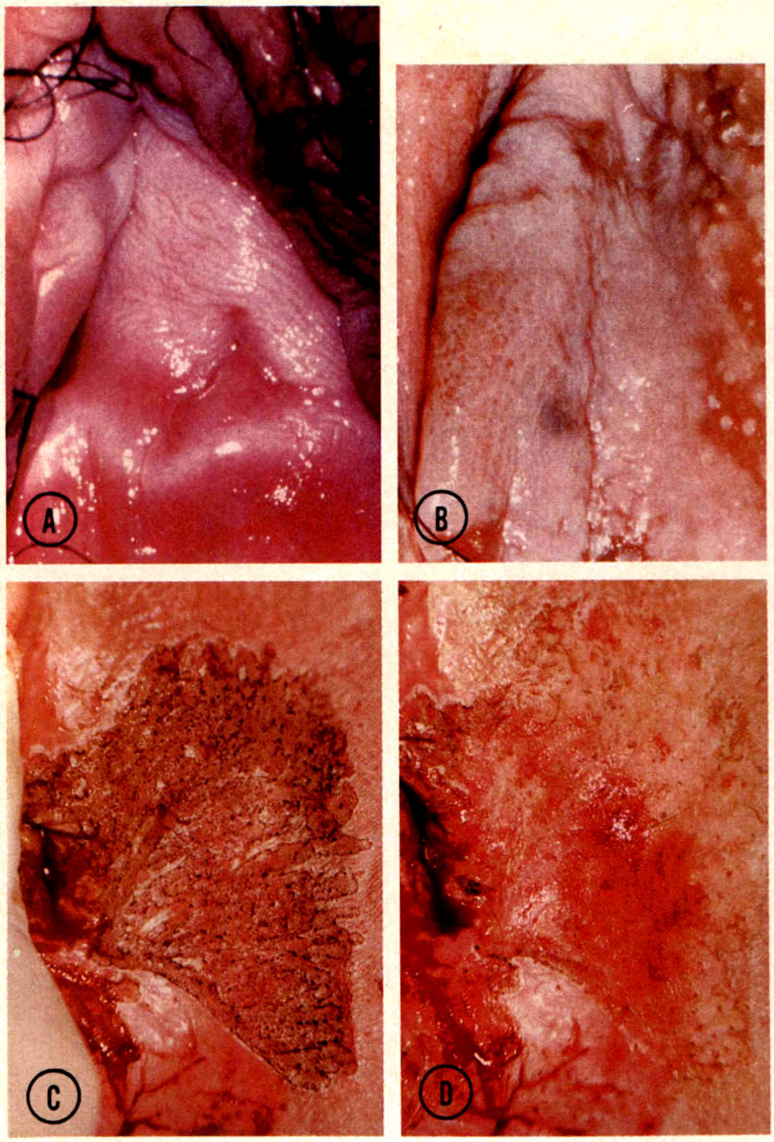

Fig. 3. *A,* Prominent acetowhitening of clinically normal, papillomavirus-infected epithelium surrounding the urethra. Despite a close resemblance to vulvar intraepithelial neoplasia, acetowhitening of subclinical papillomaviral infection is often distinguishable by its snow-white color and shiny reflectance. *B,* A colpophotograph of squamous carcinoma in situ affecting the left labium minus. In contrast to the previous figure, this neoplastic lesion shows an off-white color and a nonreflectant hue. *C,* First surgical plane. A view through the operating microscope after initial "brushing" with the laser. Beneath the charred remnants of the surface squames can be seen the refractile remnants of plump keratinocytes in the proliferating zone of the epidermis. *D,* First surgical plane, after the epithelial debris has been wiped away with a moist gauze. This maneuver exposes the intact surface of the underlying corium.

tion does not extend below the middermis, this method of treatment will yield a cosmetically pleasing end result, irrespective of the area ablated.[8] Hence, this technique is based upon three surgical principles: (1) correct identification of all areas of intraepithelial neoplasia or human papillomavirus–infected epithelium in the lower genital tract, (2) selection of a "flat" beam at an appropriate power density, and (3) an ability to exercise precise control over the depth of laser ablation.

Accurate delineation of extent of disease

The first principle is satisfied by performing a very thorough preoperative and intraoperative colposcopy of the vulva, vagina, cervix, urethra, and anus, to delineate all areas of vulvar intraepithelial neoplasia or human papillomaviral infection. Although colposcopy is most often used for the evaluation of cervical and vaginal lesions, both subclinical papillomaviral infection and intraepithelial neoplasia of the vulva can be visualized through the colposcope. However, acetowhitening of these more keratinized epithelia takes longer to develop than it does on cervical and vaginal mucosae.[9] Nonetheless, soaking the vulva with 3% to 5% acetic acid for 3 minutes (by the clock) will usually produce prominent acetowhitening of large areas of skin that appeared normal to naked eye examination.

As is the case in cervical colposcopy, acetowhitening of benign papillomaviral lesions tends to have a bright, snow-white color and a shiny reflectance (Fig. 3, *A*), whereas acetowhitening of vulvar intraepithelial neoplasia tends to have a dull, gray-white color and a nonreflectant hue[9-11] (Fig. 3, *B*). The importance of preoperative histologic evaluation of any itchy, white vulvar lesion is self-evident. However, the need (both medical and legal) to obtain representative biopsy specimens from all patients with apparent human papillomaviral infection is sometimes overlooked. Not infrequently, biopsy specimens of clinically unremarkable "condylomas" will show squamous carcinoma in situ; rarely, such lesions may even contain foci of occult invasion.

Lesions that are not clinically worrisome can be adequately assessed by multiple punch biopsy, preferably under colposcopic control. A particular search should be made for areas of abnormal pigmentation, dull acetowhitening, coarse capillary patterns, and prominent plaques or papules. Discomfort to the patient can be minimized by injecting the local anesthetic with a dental syringe, with the use of a 30-gauge needle (A. Ferenczy, personal communication). However, any areas of prominent induration or ulceration, any large or solitary nodules, and any lesions characterized colposcopically by friable yellowish epithelium or bizarre dilated capillaries must be evaluated by wide local excision, since punch biopsy cannot be relied upon to rule out occult invasion in these circumstances.[12, 13] Extreme caution must also be exercised in the triage of any long-standing condylomas or dystrophies in immunosuppressed and elderly patients.

Selection of a "flat" beam at an appropriate power density

There are two primary variables by which the surgeon can control the carbon dioxide laser: time of exposure and power density. Hence laser surgeons must have a clear understanding of the differences between energy, power, and power density. *Energy* means the capacity to perform work (for instance, heating tissue). Energy is the product of power by time and is measured in joules. *Power* refers to the rate at which work is done, measured in watts. *Power density* is the power per unit area of the focused beam, expressed in watts per square centimeter. The *volume* of tissue removed is determined by the dose of delivered energy (power × time), the *rate* of tissue removal depends mainly on power density (power per unit area).[1]

Unfocused laser beams are not suitable for surgical use. First, beams of such large diameters usually have insufficient power even to coagulate tissue. Second, even if power output was increased to an intensity that would produce tissue vaporization, any resulting incision would have a width of 1 to 2 cm. Hence, whether the laser emissions are to be deployed through an operating microscope or as a hand-held probe, a lens must be used to focus the beam to a smaller spot size, thereby limiting incision width and increasing effective power at the impact site.[1]

A given dose of energy can be delivered by using high power for a short time, average power for an average time, or low power for a long time. *At the impact site,* a given amount of radiant energy will destroy the same volume of tissue, irrespective of the speed at which it was delivered. However, the extent of thermal coagulation *at the crater margin* is profoundly influenced by the speed of energy delivery. Most of the thermal necrosis at the crater margin is produced by lateral heat conduction from the impact site. Low power densities increase the thickness of the zone of thermal necrosis in two ways.[2] First, by taking longer to vaporize the same tissue volume, the surgeon increases the time during which heat will flow to surrounding areas. Second, power densities that are too low for rapid vaporization produce desiccation and carbonization of the crater base. Continued irradiation will heat this anhydrous char to >400° C, thereby further increasing heat conduction to surrounding tissue. Thus surgeons who use suboptimal power densities and continue to irradiate charred surfaces violate every principle of laser surgery. In effect, such unskilled surgeons are just using the laser to produce a conduction burn to underlying structures. Under such circumstances, the visible extent of surface vaporization will greatly underestimate the actual extent of tissue death.

For a laser of a given wavelength, power density is the most important determinant of tissue effect. Since the area of a circle varies according to the *square* of the radius, an increase in spot diameter will result in an exponential decrease in power density. For surgical situations, average power density is most easily approximated by the formula

$$PD = \frac{100 \times W}{D^2} \text{ watts per square centimeter}$$

where W = the power output shown by the in-line power meter on the laser console (in watts), and D = the measured diameter of the imprint left by a 10 watt, 0.1 second pulse on a moistened tongue depressor (in millimeters).

Bioeffects in vivo are further modified by local cir-

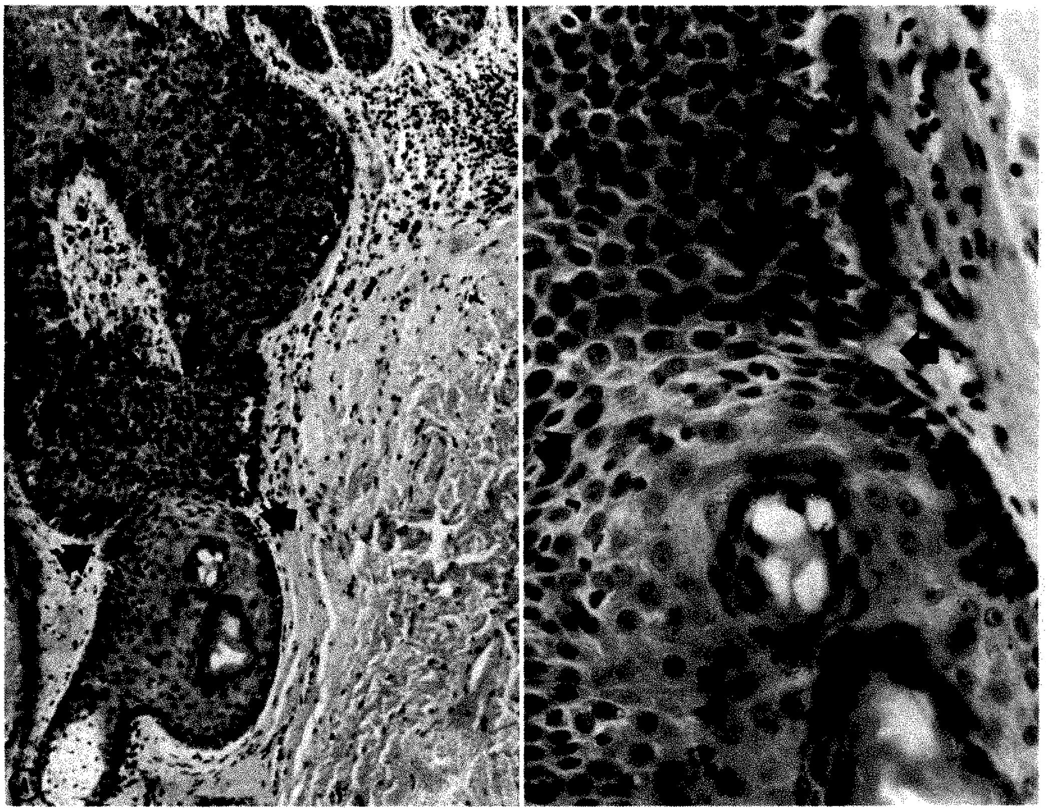

Fig. 4. Squamous carcinoma in situ of the fourchette, extending down the pilosebaceous ducts. The arrows point to the sharp junction between neoplastic cells (in the duct) and normal glandular epithelium. (Hematoxylin and eosin stain. *A*, ×50; *B*, ×400.)

Table I. Suggested power densities for the carbon dioxide laser ablation of different areas in the lower genital tract, according to the experience of the operator

	Power density (W/cm^2)		
Surgical situation	*Expert*	*Experienced*	*Novice*
Cervical transformation zone	1500	1000	750
Cervical portio and vaginal walls	1200	800	*
Keratinized areas of vulva and perineum	800	600	*
Nonkeratinized vulvar mucosae; anus and urethra	600	450	*

*Less experienced laser surgeons are advised not to use the carbon dioxide laser in these sites.

culation and density of tissue. Local circulation is important because blood flow both cools the tissues and replenishes some of the vaporized extracellular fluid.[14] Density is important because tissues vary in their resistance to laser vaporization, according to their water content and protein structure. Hence, accuracy of depth control must take account of the need for different power densities at different anatomic sites. Since cervical and vaginal stroma have a high content of extracellular water, the operator will need moderate to high intensities (750 to 1500 W/cm^2) to overcome the "stromal heat sink" at these sites.[15] In contrast, vulvar and anal mucosae are fragile tissues with relatively low circulations. While it is logical to always use high power densities, experience has shown that power densities of >600 W/cm^2 are very difficult to control on the vulva (Table I).

Power density describes the average power density within the focal spot. In reality, there are major variations in beam intensity within the focal spot. In an ideal laser, beam intensity is maximal at the center and falls off exponentially in all directions.[2] Hence the intensity profile resembles a three-dimensional guassian curve. Crater shape mirrors energy distribution of the

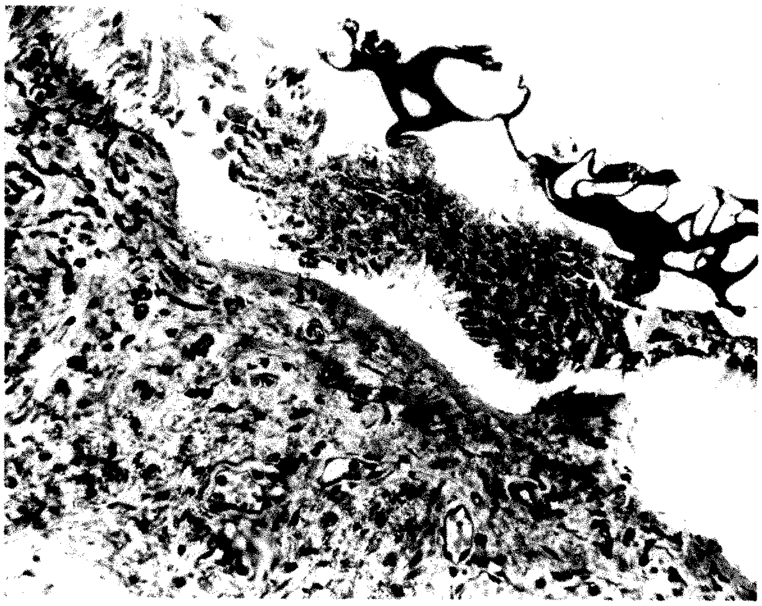

Fig. 5. First surgical plane. Low-power photomicrograph, showing how a rapid brushing action can limit the zone of vaporization to the epidermal surface. Hence, the zone of thermal necrosis lies within the proliferating layers of the epidermis, and the superficial dermis is almost completely spared. The dark, amorphous aggregates at the surface represent fused keratin molecules. Beneath this melted keratin is a group of heat-denatured prickle and basal cells that have been detached from the underlying basement membrane. (Methylene blue. × 100.)

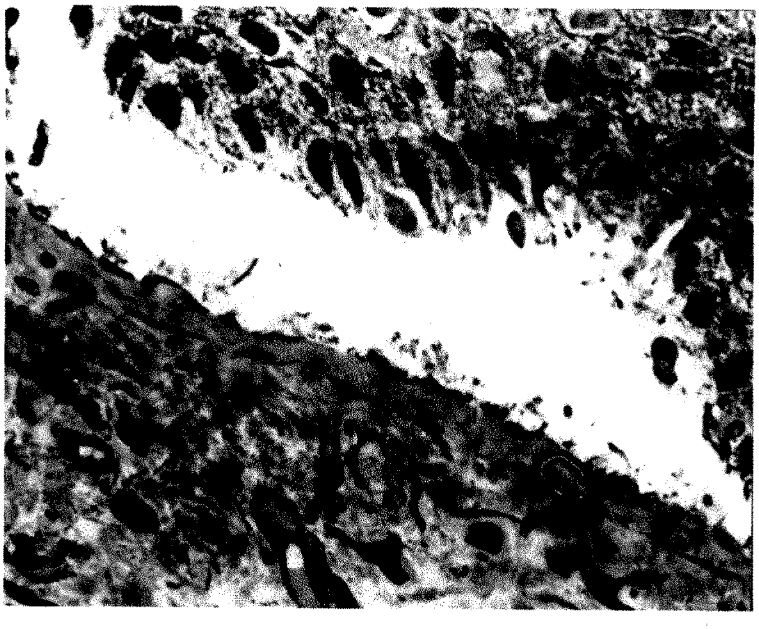

Fig. 6. First surgical plane. High-power view, showing how the heat-denatured epidermal cells have lifted off the underlying corium, leaving remnants of the hemidesmosomes attached to the basement membrane. In this field, the zone of thermal necrosis extends about 20 μm into the papillary dermis. The junction between the zones of thermal necrosis and sublethal injury is subtle, but discernible. (Methylene blue. ×400.)

incident beam. Hence a beam with a gaussian mode will produce a crater shaped like an ice cream cone. Gaussian profiles are ideal if the laser is to be used as a thermal scalpel but create difficulty when the therapeutic objective is to ablate a large area of tissue to a uniform depth. For epithelial ablation, the best beam profile is a converging beam that is sufficiently defocused as to produce a hemispherical rather than a conical crater. This is most easily achieved by setting the operating microscope such that the laser beam is fo-

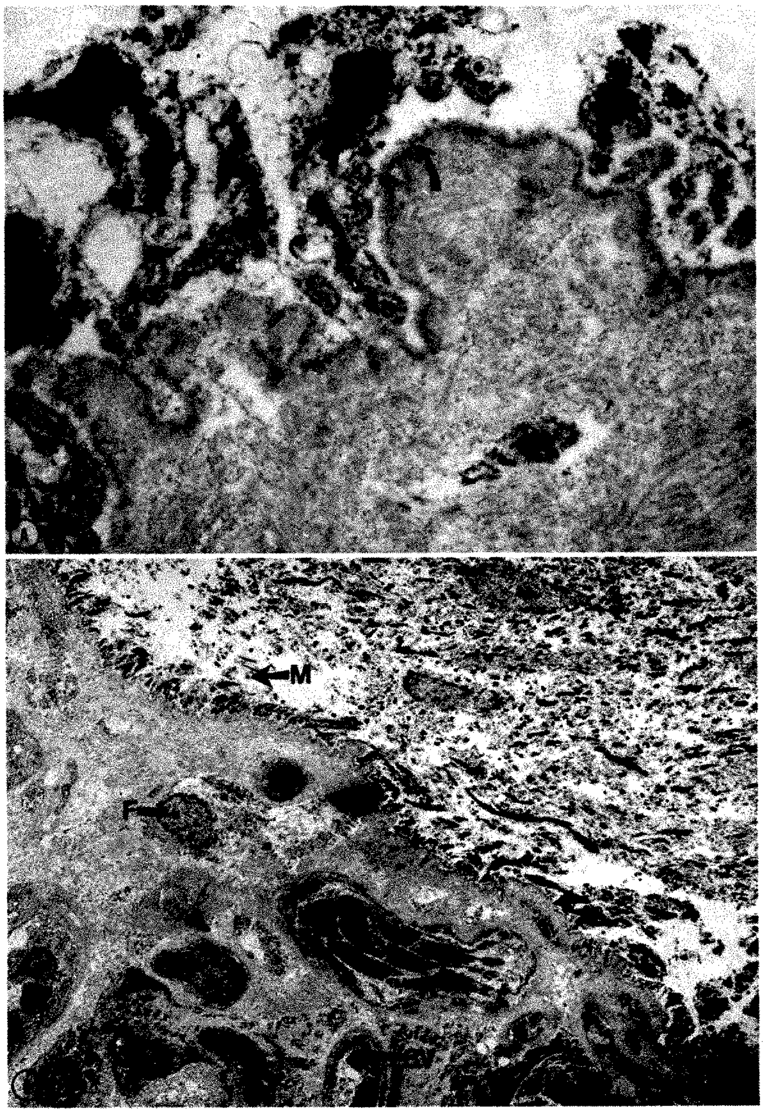

Fig. 7. First surgical plane. *A*, Low-power electron micrograph demonstrating the totally disrupted epithelium lifting off the basement membrane *(arrow)*. Although damaged, the fibroblasts *(F)* and blood vessels *(BV)* of the dermis have suffered less destruction than the cells of the epithelium. The black granules *(M)* are denatured, but structurally intact melanocytes. (× 2240.) *B*, High-power view from an area of apparent attachment. Even when the epidermis remains closely apposed, a plane of cleavage is still apparent *(arrows)*. Although denatured, the basement membrane is still recognizable. (× 28,400.)

cused at 400 mm, while using visual optics that focus at 300 mm. In practice, beam profile is easily checked by firing the laser into a raw egg white and examining the shape of the resultant crater.

Control of depth by preservation of anatomic orientation

The first step in control of depth is to understand that the level of ablation must be varied according to the disease being treated. Although surface keratinocytes in vulvar intraepithelial neoplasia may grow downward and displace adnexal keratinocytes from hair follicles or sebaceous glands,[16] such pilar extensions are said not to occur in benign condylomas.[8] Hence, the depth of ablation for vulvar intraepithelial neoplasia should always include the pilosebaceous ducts (Fig. 4). In contrast, laser destruction of even the most refractory or extensive human papillomaviral infection should not extend beneath the basement membrane. Perhaps the best approach to the treatment of vulvar intraepithelial neoplasia is for the surgeon to carefully examine the histologic sections. Any areas that show extension of neoplastic epithelium below the level of the middermis are best managed by wide linear excision or subtotal vulvectomy, with the laser reserved for the treatment of any surrounding foci of more superficial disease.

Limiting the depth of ablation to these levels is not

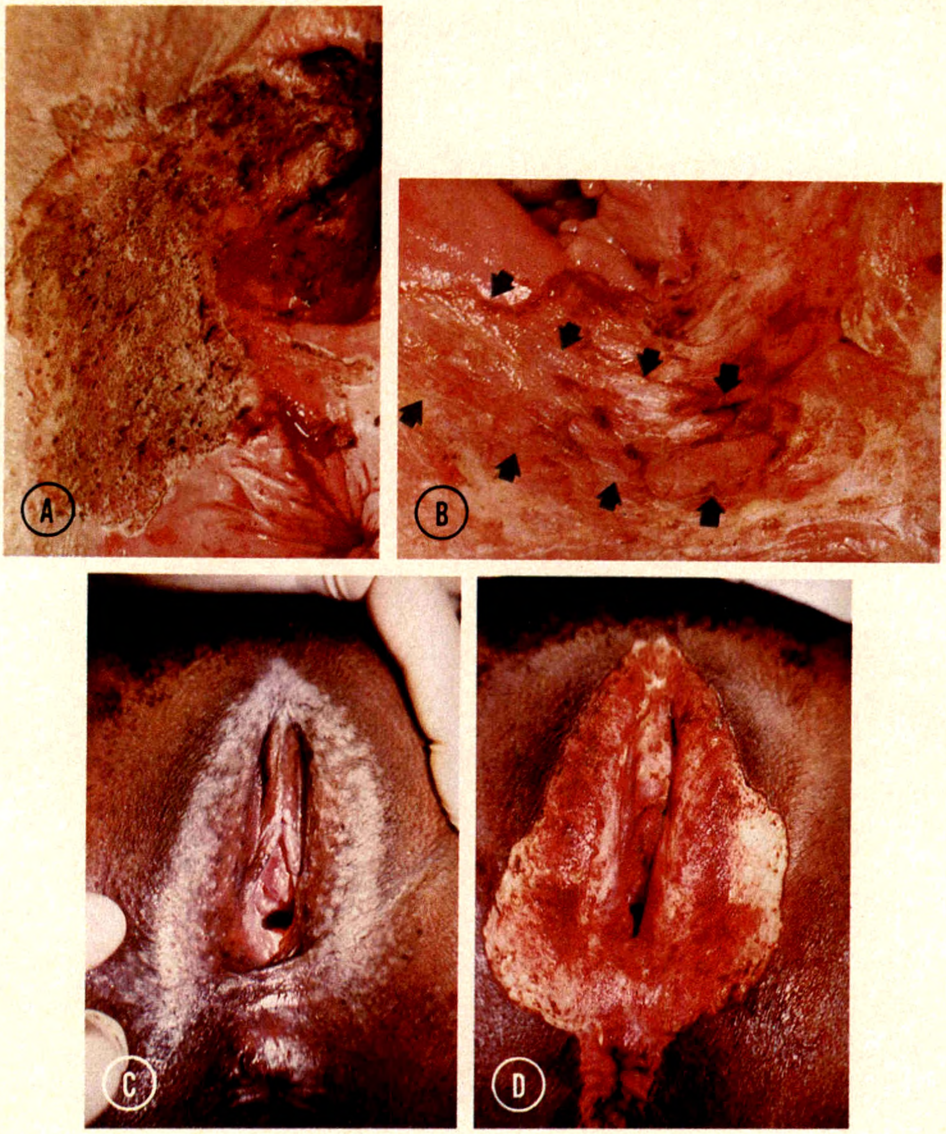

Fig. 8. *A,* Second surgical plane. The exposed papillary dermis has been gently relased, sufficient to scorch the surface without causing extensive vaporization. *B,* Third surgical plane. A slower, more deliberate relasing of the exposed corium. This maneuver has vaporized the dermal surface, revealing the coarse collagen and elastic bundles of the reticular dermis *(arrows). C,* Hyperplastic dystrophy of the vulva, seen as diffuse whitening even without application of acetic acid. *D,* The end result of superficial laser vulvectomy to the first surgical plane. Provided that the surgeon can control the depth of penetration, large areas of abnormal epithelium can be ablated with impunity. In this patient, healing occurred within 2 weeks, with an end result that was entirely indistinguishable from normal vulvar skin.

so easy as one would think. After the first impact of the laser, the wound is immediately covered by a layer of char that precludes depth orientation.[3] Most laser surgeons counteract this problem by making visual estimates of crater depth. However, since vulvar epidermis is only 100 to 200 μm in thickness, this makeshift method leads to uncertain control of depth and frequent penetration of the basement membrane.

A much better method is to preserve anatomic orientation by wiping away the surface char, and then using the visual characteristics of different levels of tissue as a means for precise control of depth.[3] By means of this technique, four characteristic surgical planes are identifiable. Application of the laser beam to the deepest plane requires skin grafting, and is described elsewhere (Reid, report in preparation).

First surgical plane. Application of the laser beam through the opaque surface of the skin (consisting of compressed, anucleate, keratinized squames) uncovers the plump keratinocytes of the prickle and basal layers

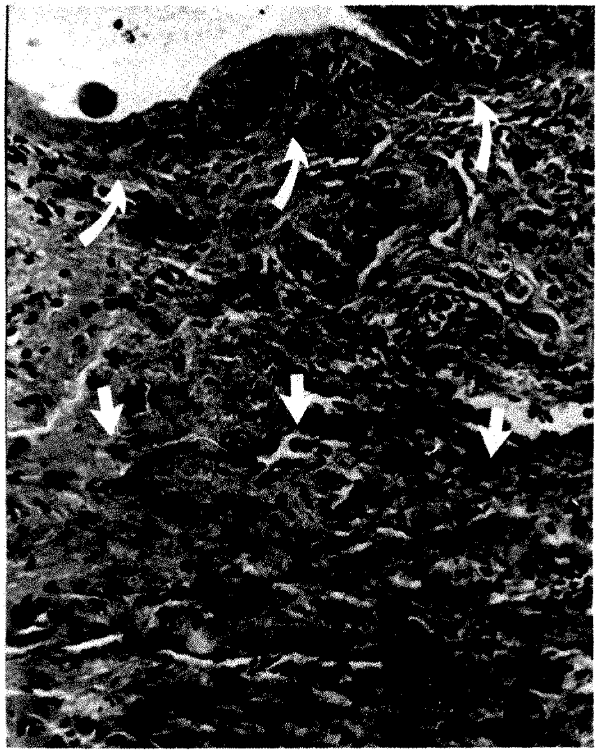

Fig. 9. Second surgical plane, showing how the zone of vaporization *(curved arrows)* has been deepened to include a portion of the papillary dermis. The zone of thermal necrosis lies in the lower portion of the papillary dermis. The underlying reticular dermis *(straight arrows)* shows only minor thermal injury, with no evidence of coagulation necrosis. (Methylene blue. ×200.)

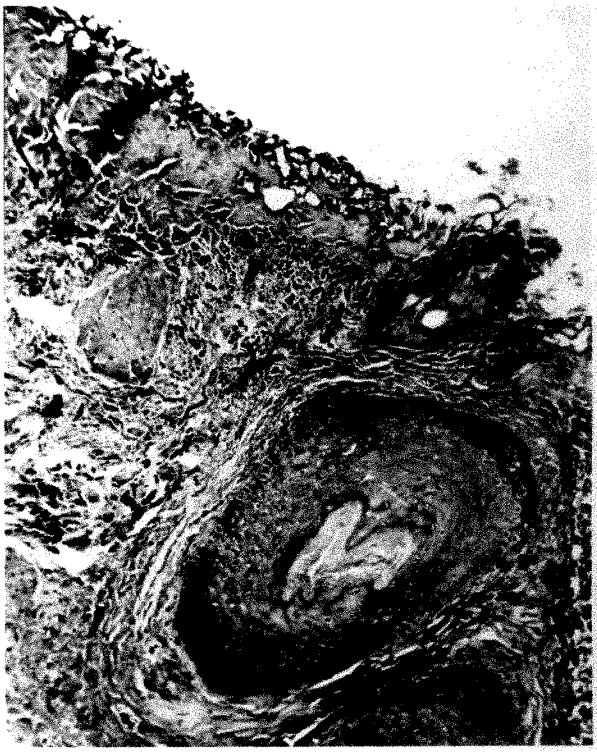

Fig. 10. Third surgical plane. The zone of vaporization lies within the reticular dermis. A small hair follicle is encompassed by the zone of thermal necrosis in the crater base. Beneath this 100 μm layer of denatured dermal proteins, viable sweat glands and hair follicles can be seen. (Methylene blue. ×200.)

(Fig. 5). Penetration to the correct level is accomplished by rapid oscillation of the micromanipulator, so that the helium neon spot describes a roughly parallel series of lines. The individual beam paths should be close to each other, without overlapping, much as a child would "color in" with a crayon. When done correctly, each of these lines will show bubbles of silver opalescence beneath the surface char (Fig. 3, *C*), and the maneuver will be accompanied by a distinctive crackling sound. Inadvertent penetration of the dermis is signaled by the loss of these two characteristic signs.

Placing the zone of vaporization at the level of the proliferating layer seriously damages the basal cells, and produces a plane of cleavage from the basement membrane. This separation may be sufficiently pronounced as to be visible through the light microscope (Fig. 6) or so subtle that it can be detected only through the electron microscope (Fig. 7). The speculation is that this plane of cleavage is produced by marked differences in thermal shrinkage, which act to shear the epidermis from the dermis. Whatever the case, it is a very fortuitous effect, because any remaining basal cells can be easily removed by simply wiping them away with a moistened gauze square. This maneuver exposes the smooth surface of the basement membrane, beneath which can be seen the anatomically intact papillary dermis (Fig. 3, *D*). Although lasing to this depth does not produce any obvious photophysical disruption of the corium, a very shallow layer of coagulation necrosis will form on the dermal surface over the succeeding week (Fig. 6). Beneath this coagulum is a zone of sublethal thermal injury that extends about another 80 μm beneath the remnants of the basement membrane. Such wounds heal completely within 14 to 21 days, and yield an end result that is entirely indistinguishable from normal vulvar skin.

Second surgical plane. Gentle reapplication of the laser beam to this smooth white surface, sufficient to scorch the surface without producing significant tissue vaporization, will uncover relatively homogeneous yellowish tissue that resembles a chamois cloth (Fig. 8, *A*). This appearance reflects the histologic composition of the papillary dermis, namely, thin collagen bundles that interlace with a fine network of reticular and elastic fibers, all of which are dispersed in a relatively cellular matrix. Application of the laser beam to this point deepens the zone of coagulation necrosis to include a large portion of the papillary dermis, with only minor thermal injury to the underlying reticular dermis (Fig. 9). Such wounds are also followed by rapid healing and a cosmetically pleasing end result.

Third surgical plane. Cutting deeper than the upper quarter of the corium will expose the reticular dermis, which corresponds to the portion of animal skin from which leather hides are made. The reticular dermis consists of a network of coarse collagen bundles and thick elastic fibers, dispersed within a relatively acellular matrix. Ablation to the middle of the reticular dermis uncovers these coarse collagen and elastic bundles, which are visible through the operating microscope as gray-white fibers that resemble water-logged cotton threads (Fig. 8, *B*). This third surgical plane (Fig. 10) is the deepest level from which optimum healing will result. Provided that penetration can be confined to this plane, the surgeon can ablate large areas with relative impunity (Fig. 8, *C* and *D*).

Most of the hair follicles and apocrine glands are located within the lower half of the reticular dermis. Application of the laser beam beyond the middermis is signaled by the uncovering of the skin appendages, which, through the operating microscope, look like tiny grains of sand. Unfortunately, when the depth of ablation is sufficient to expose these tiny granules, many of the skin appendages will already have suffered lethal damage. Therefore, healing from such a depth will be slow and will produce a scar that is markedly different from normal vulvar skin.[3] Moreover, application of the laser beam beyond the desired plane can result in hypertrophic scarring or keloid formation. Inadvertent destruction of most or all of the skin appendages will produce an effective third-degree burn. Such wounds heal by granulation from the base and by epithelial ingrowth from the sides, and yield atrophic, colorless scars that are devoid of physiologic skin functions[3] and too weak to withstand vigorous coital friction.

Comment

The carbon dioxide laser resembles the hot cautery, the electrodiathermy, and the cryosurgical probe, in that all are instruments of thermal destruction. However, with the carbon dioxide laser, the surrounding zones of thermal necrosis and thermal injury can be reduced to very narrow and sharply defined bands. By contrast, the unwanted thermal injuries produced by the other three instruments are much more diffuse and very hard to control. Nonetheless, the potential for surgical advantage is easily dissipated by unskilled use. The margin between an excellent versus a poor result is a narrow one. Unless the surgeon uses optimum power densities and special techniques to control depth, he will not obtain an optimum outcome on the vulva.[9]

Too high a power density will make the laser uncontrollable, and produce a wound that is characterized by an irregular pattern of ridges and gutters. Penetration at the base of the gutters is usually excessive, whereas destruction at the top of the ridges may be inadequate. Paradoxically, the selection of too low a power density also detracts from the surgical advantage, by altering the relationship between immediate and delayed effects. Hence, good surgical control with a minimum of unwanted thermal damage depends upon the ability to use the highest appropriate power density.

Does superficial laser vulvectomy work by destroying all infectious particles? Certainly, a conscientious attempt was made to ablate all areas of human papillomaviral infection. However, despite the large areas treated, one must question whether it is likely that a surgeon could locate and destroy *every* infected cell. Perhaps part of the explanation may be that regeneration from the skin appendages produces an epithelium that is less susceptible to human papillomaviral reinfection. Surface and adnexal keratinocytes come from different embryologic stem cells.[16] Since adnexal keratinocytes appear resistant to human papillomaviral infection in vivo,[8] much of the success may be due to the fact that the new surface epithelium derives mainly from the skin appendages.

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Continuous long-term intravenous β-sympathomimetic tocolysis

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This report concerns the clinical course and outcome of 16 patients treated by continuous long-term intravenous β-sympathomimetic tocolysis (≥1 week's intravenous therapy). Half of the patients received such therapy for at least 5 weeks. Intravenous tocolysis was adjusted to decrease uterine activity and maintain a satisfactory pulse and blood pressure. Parenteral tocolysis was continued until there was a successful transition to oral therapy, until fetal maturity, or until maternal/fetal indications for delivery were noted. Data indicate that the cardiovascular and metabolic effects were pronounced mostly during the first 3 to 4 days of therapy and then returned toward pretreatment values. In none of the study patients was the treatment discontinued because of drug-related problems, electrocardiogram changes, chorioamnionitis, or fever. The experience indicates that, in a selected group of patients and under close supervision, continuous long-term intravenous β-sympathomimetic tocolysis may be considered a safe therapeutic modality able to prolong pregnancy with a more desirable outcome. (AM J OBSTET GYNECOL 1985;152:271-4.)

Key words: β-Sympathomimetics, tocolysis

Most of the reported serious cardiovascular complications associated with β-adrenergic–agonist tocolysis have occurred during the parenteral administration of these agents. These side effects, which include pulmonary edema and myocardial ischemia, were usually diagnosed after 24 hours of treatment.[1] Thus it was recommended that parenteral tocolysis be replaced by oral medication within 12 to 24 hours.[2] While such a therapeutic protocol is efficacious in many cases, our experience has shown that in 3% of our treated patients intravenous tocolysis could not be replaced by oral medication without the recurrence of frequent uterine contractions, resulting in additional cervical changes. In this group of patients, the choice was between continuous long-term (≥1 week) intravenous tocolysis and a high likelihood of preterm delivery with its grave neonatal consequences. Since the use of long-term intravenous β-mimetic therapy is controversial, there are only a few reports on the safety and efficacy of such therapy and none of them includes the agents most commonly used in the United States.[3, 4] The purpose of this report is to describe our experience with continuous long-term intravenous ritodrine tocolysis in a group of patients who seemed to need such an unusual approach to therapy in order to maintain their pregnancies.

Material and methods

Sixteen women having preterm labor between 24 and 32 weeks' gestation are the subject of this report. The

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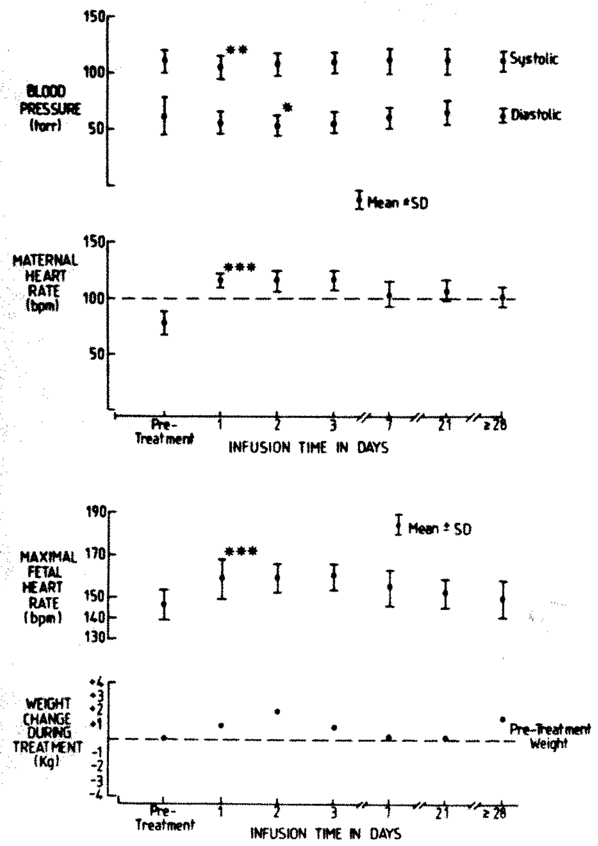

Fig. 1. Mean and standard deviation of cardiovascular and weight change values during long-term intravenous tocolysis. The level of significance of the change from pretreatment to peak treatment values is indicated by the asterisk(s): $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

clinical features of the patients are shown in Table I. Each of these women developed strong, regular uterine contractions (six or more per hour) accompanied by progressive cervical effacement and dilatation. When attempts to replace the intravenous administration of ritodrine by oral medication were made, strong and frequent contraction (five or more per hour) recurred with additional cervical changes. The goal of tocolysis in these patients was to achieve four or less uterine contractions per hour. In order to achieve this end point, the infusion rate was increased by 50 μg/min every 20 minutes as long as the pulse rate did not exceed 130 bpm for more than 2 hours and the systolic/diastolic arterial blood pressures were not lower than 80/40 torr. Attempts to reduce infusion rates and start oral maintenance were made after adequate control of uterine activity (four contractions or less per hour) was present for 12 to 24 hours. To observe these criteria and try to reach the previously mentioned end point, intravenous ritodrine therapy had to be continued at doses between 100 and 500 μg/min in 11 patients. In five patients, intravenous magnesium sulfate was added to the ritodrine at infusion rates of 1 to 3 gm/hour because of the maternal heart rate response, which exceeded 130 bpm for more than 2 hours, thus necessitating a reduction in ritodrine infusion rate. Parenteral tocolysis was continued until one of the following occurred: (1) There was a successful transition to oral therapy; (2) a mature fetal lung profile was demonstrated; (3) gestational age was >36 weeks; (4) there was a maternal or fetal indication for delivery.

Table I. Clinical features of patients

Maternal age (yr)	30 ± 4*
Primiparous (n)	11
Multiparous (n)	5
Singleton fetus (n)	12
Twins (n)	3
Triplets (n)	1
Cervical dilatation at onset of intravenous therapy (cm)	0.7 ± 0.6*
Cervical effacement at onset of intravenous therapy (%)	56 ± 19*

*Mean ± SD.

Surveillance of these patients in the high-risk pregnancy unit included careful and frequent monitoring of maternal vital signs (hourly), weight changes (daily), fetal heart rate (every 8 hours), electrocardiograms (before treatment, daily for 3 days, then weekly), fluid intake and output (daily), hemoglobin and hematocrit (before treatment, daily for 3 days, then weekly), and plasma glucose and serum potassium levels (before treatment, daily for 3 days, then weekly). Potassium was administered orally where serum concentrations were <2.5 mEq/L. Total daily oral and parenteral fluid intake was limited to 2000 ml.

The results are expressed as means ± 1 SD. The significance of differences between means prior to and during therapy was evaluated by analysis of variance for repeated measures.

Results

The cardiovascular and metabolic responses to continuous intravenous tocolysis are presented in Figs. 1 and 2. These data clearly show that the changes were pronounced mostly during the first 24 to 96 hours of therapy, after which there was a return toward pretreatment values. The maximum response occurred invariably after 48 hours. Of note is the fact that maternal heart rate, albeit showing a lesser response after 96 hours, remained at approximately 100 bpm throughout therapy. This sustained tachycardia is thus probably indicative of the presence of adequate tocolytic concentrations. Similar but less pronounced effects could be seen in fetal heart rate responses. Duration of intravenous tocolysis and gestational age at delivery are given in Table II. Of the 16 patients in this study, 10

Table II

Gestational age when intravenous therapy started (wk)	27 ± 3*
Gestational age when intravenous therapy stopped (wk)	32 ± 3*
Duration of intravenous therapy (wk) (range 1-12)	5 ± 3*
Gestational age at delivery (wk)	34 ± 4*
Received betamethasone (n)	12
Eventually transferred to oral therapy (n)	7
Attained ≥ 36 weeks' geatational age (n)	10

*Mean ± SD.

(62.5%) were delivered of their infants after 36 completed gestational weeks. In four patients, in spite of continuous therapy, slow progressive cervical dilatation or rupture of the fetal membranes resulted in spontaneous preterm delivery. In the remaining two women tocolysis was discontinued because of preeclampsia in one patient and because of evidence of fetal lung maturity in the other. Twelve patients (75%) received two intramuscular injections of betamethasone, 12 mg each. Of these 12 patients, six were delivered prior to 36 completed gestational weeks. There was no maternal or neonatal evidence of infection (clinical, histologic, cultures) in any of the study patients.

Of the 21 newborn infants in this study, four suffered from mild respiratory distress syndrome and nine received phototherapy for mild hyperbilirubinemia. The mean neonatal stay in the intensive care nursery for these neonates was 5 ± 2 days. All infants were eventually discharged and at 6 months of age were found to be doing well. In all patients, labor and delivery followed within 24 hours after discontinuation of therapy, thus probably supporting the accuracy of the diagnosis of preterm labor.

Comment

The current approach to β-adrenergic tocolysis includes an initial, short-term parenteral drug administration that is replaced within 12 to 24 hours by oral medication. In the absence of contraindications, oral administration of these agents is continued until either fetal maturity has been reached or until resumption of parenteral therapy is indicated by relapse to preterm labor. Since almost all the reported serious side effects of tocolysis occur during parenteral therapy, this approach provided for both patients' safety and their convenience, by enabling ambulatory outpatient care during oral treatment.

In approximately 60% of patients, even a low infusion rate of 50 μg/min provides adequate control by producing a serum ritodrine concentration of 15 to 31 ng/ml.[5] Oral therapy produces lower serum concentrations, which may in certain patients be too low to control uterine contractions. Maintenance of such patients, who require higher concentrations of ritodrine, on a regimen of oral medications may result in additional progressive cervical changes. As these cervical changes advance, the need for higher infusion rates to control uterine activity during subsequent treatment courses will increase[5] and the likelihood of successful tocolysis may decrease. It is for these patients that continuous parenteral tocolysis may prove beneficial if the safety of this treatment modality can be established.

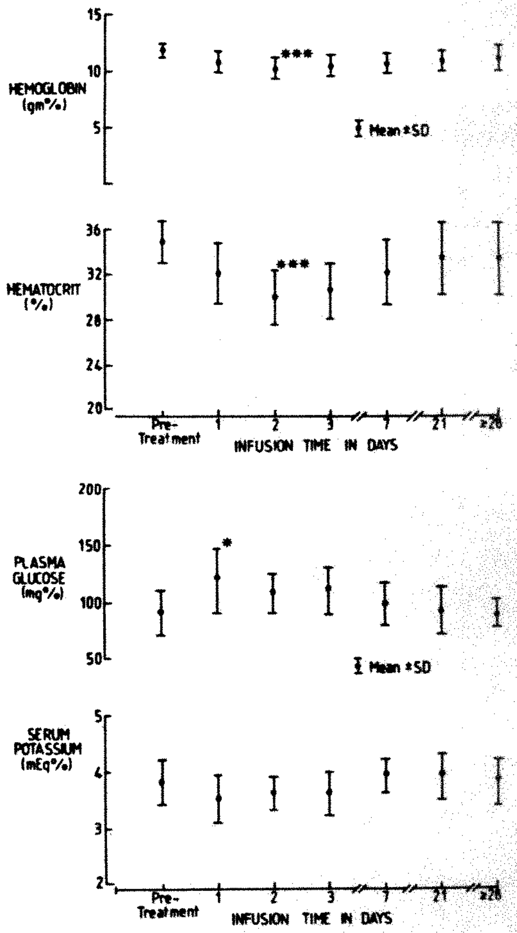

Fig. 2. Mean and standard deviation of metabolic values during long-term intravenous tocolysis. The level of significance of the change from pretreatment to peak treatment values is indicated by the asterisk(s): *p < 0.01; ***p < 0.001.

Review of the literature and experience from this institution reveal that the complications of β-adrenergic tocolysis occurred almost exclusively within the first 24 to 96 hours of parenteral therapy.[1, 2] As our data from this study demonstrate, this is also the period of metabolic and cardiovascular adaptation. It is conceivable that after this critical interval, when most of the measured variables return toward pretreatment values, the risk for complications is significantly reduced. Therefore patients with frequent recurrences of preterm labor during oral therapy, who are repeatedly exposed to this critical adaptation interval, may be at less risk of complications by having continuous intravenous tocolysis. Particular relevance to this issue is the report by Caritis et al.,[5] who noted that the cardiac response during β-adrenergic tocolysis relates to the rate of change in the infusion rate rather than to the absolute concentration of ritodrine in the plasma. This observation would then imply that in a group of patients like ours, who require high but steady infusion rates of ritodrine, the likelihood of side effects is expected to be less than that in patients who have frequent recurrences of preterm labor during oral maintenance.

A second important issue is the possible development of myometrial tachyphylaxis to ritodrine, leading to progressively increasing infusion rates. Such tachyphylaxis, with a blunted response to β-adrenergic agonist stimulation, was observed in relationship to cardiac response[5] but has not yet been shown to concern uterine activity. It is nevertheless possible that, when examined in larger series, continuous exposure of the pregnant uterus to high ritodrine concentrations may result in tachyphylaxis. Therefore, in order to maintain the lowest effective infusion rates, the end point of tocolysis in our patients was not the elimination of all contractions but rather the decrease of their frequency to four to five contractions per hour.

Finally, the question of fetal safety during continuous parenteral adrenergic tocolysis must be considered. Crawford et al.[6] found a thicker ventricular septum in echocardiograms of neonates who were exposed to isoxsuprine in utero.[6] However, in a recent report by Hendricks et al.[7] on fetal and neonatal echocardiograms during and after long-term β-adrenergic tocolysis, cardiac dimensions were found to be normal when adjusted for weight. The currently available information on the fetal safety of either short- or long-term ritodrine tocolysis is as yet insufficient to establish their absolute safety, but it seems that the benefit of preventing prematurity justified their use.

This report suggests that for a selected group of patients who cannot undergo discontinuation of parenteral tocolysis without a serious risk of immediate preterm delivery, the option of continuous intravenous tocolysis should be considered. Furthermore, our results, which were favorable in a limited number of such patients, seem to indicate that further exploration of such therapeutic regimens in larger samples should be carried out.

We acknowledge the statistical analysis of the data by Anne C. Burr, M.Ed.

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Immunoperoxidase localization of chlamydial antigens in acute salpingitis

Barbara Winkler, M.D., Werner Reumann, M.D., Masaru Mitao, M.D., Leza Gallo, M.D., Ralph M. Richart, M.D., and Christopher P. Crum, M.D.
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Seventy surgically excised fallopian tubes in which there was originally a diagnosis of acute salpingitis were reviewed histologically and screened for chlamydial antigens by the immunoperoxidase technique. Chlamydial antigens were localized within tubal epithelial cells in two of the 70 cases (3%). Endometrial specimens from these two patients were also positive for chlamydial antigens. There was no definite correlation between the histologic features of the salpingitis and chlamydial immunoperoxidase positivity. (AM J OBSTET GYNECOL 1985;152:275-8.)

Key words: Salpingitis, *Chlamydia*, immunoperoxidase technique

Chlamydial infection has increasingly become recognized as a cause of acute salpingitis, chronic pelvic inflammatory disease, and infertility. It is now estimated, with the use of serologic and culture methods, that 20% to 50% of cases of acute salpingitis are chlamydia-related and that the incidence, prevalence, and postinfectious complications of chlamydial infections may exceed those of gonorrhea.[1] The relationship between chlamydial salpingitis and concomitant cervical or endometrial infection, and subsequent infertility, is the subject of much current investigation.

The accurate diagnosis of chlamydial salpingitis is hampered by the difficulty in obtaining appropriate tissue for culture. Although ascending infection may be suggested by a positive culture of the endocervix or endometrium, a negative endocervical or endometrial culture does not rule out the presence of tubal chlamydial infection. Inflamed fallopian tubes are often encountered during laparoscopy or laparotomy for pelvic pain, pelvic inflammatory disease, tubo-ovarian abscess, and ectopic pregnancy. Although intraoperative specimens for culturing are obtained from accessible tissues, e.g., exudate, pelvic fluid, or serosal surfaces, these samples may not be optimum for the isolation of the obligate intracellular and intraepithelial chlamydial organisms. Chlamydial cultures of tubal epithelium are seldom obtained even when salpingectomy is performed.

The recent availability of specific heterologous antisera has allowed immunoperoxidase localization of chlamydia-infected cells, and we previously reported on the application of this technique to samples of tissue from the endocervix and endometrium.[2-4]

We now report a histologic and immunohistochemical analysis of 70 cases of acute salpingitis examined for the presence of chlamydia. The goals of the study were to determine the efficacy of the immunoperoxidase technique in localizing chlamydial antigens in salpingitis and to characterize the cytologic and histologic findings in chlamydial infection of the fallopian tubes.

Material and methods

Fallopian tubes from patients with a diagnosis of acute salpingitis were accessioned from the files of the Division of Obstetrical and Gynecological Pathology of the Columbia-Presbyterian Medical Center for the years 1979 through 1983, and were reviewed for the presence, extent, and distribution of inflammatory infiltrate and cytoplasmic vacuolization of inclusions suggestive of chlamydia within tubal epithelial cells. Fallopian tubes with chronic salpingitis or those removed for ectopic pregnancy were not included in this analysis.

All of the specimens were stained for chlamydial antigens by means of a heterologous antichlamydial antibody against mixed sera types A-K and lymphogranuloma venereum 1, 2, and 3 generated in rabbits. The antibody was kindly provided by Dr. Jan Lindeman. A modified peroxidase/antiperoxidase technique was used with the avidin-biotin system to enhance staining, as previously described. Lymphogranuloma venereum–infected Hela cells prepared as a cell pellet and processed as a cell block served as positive controls. Cases with a dark brown precipitate were designated as positive, and the site and localization of the positive staining were recorded. The endometrial specimens from positive tubal cases, when available, were also

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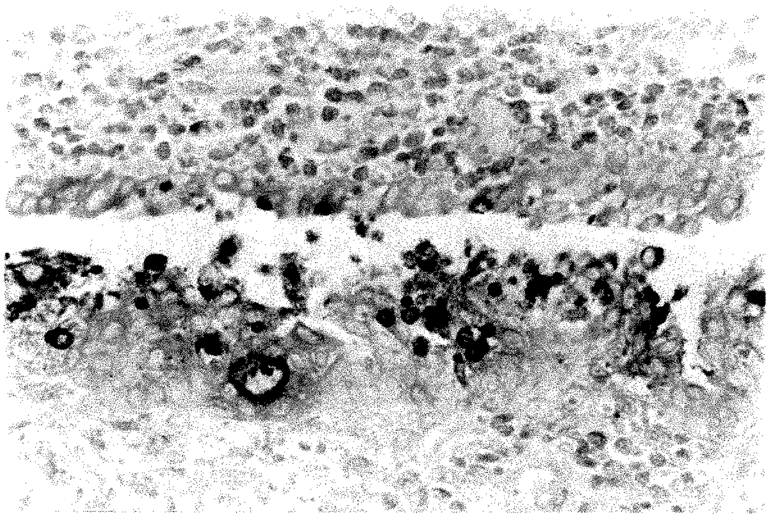

Fig. 1. Immunoperoxidase localization of chlamydial antigens in fallopian tube epithelium. Positive staining is indicated by the black precipitate which highlights rounded intracytoplasmic vacuoles that contain discrete particles.

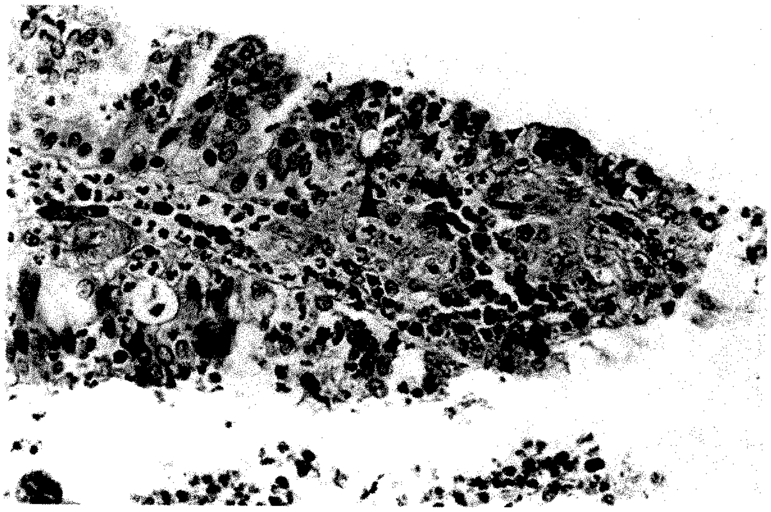

Fig. 2. Corresponding hematoxylin and eosin–stained section from an area of immunoperoxidase positivity. The tubal epithelium contains numerous neutrophils. A pale, intracytoplasmic vacuole *(arrow)* is seen corresponding to the chlamydial inclusions identified by immunoperoxidase staining.

stained for chlamydial antigens by the immunoperoxidase technique.

The clinical records of patients with positive staining were reviewed for reproductive history, symptoms, clinical findings, clinical evidence of cervical or endometrial infection, history of other sexually transmitted diseases, chlamydial cultures, and therapy.

The files of the Department of Microbiology were reviewed for cases in which there had been culturing for chlamydia.

Results

Histologic and immunohistochemical findings. Seventy fallopian tubes were studied. In all cases, an extensive, severe, acute inflammatory infiltrate was present in the tubal lumen, with transmural involvement. Additional findings included variable numbers of scattered plasma cells and lymphoid cells. There was extensive necrosis and remodeling of the tubal epithelium in all cases, with disruption of the epithelial surface and the presence of glandular lumens within the tubal wall indicative of follicular salpingitis. Definite chlamydial inclusions could not be identified in any hematoxylin and eosin–stained sections prior to immunoperoxidase staining.

In only two cases (3%) was staining positive for chlamydial antigens, but the immunoperoxidase staining was extensive in both. Positive cells were found among

Table I. Summary of clinicopathologic and immunohistochemical findings in the two positive cases

Patient	Operative specimen	Pathologic findings	Immunoperoxidase positive
1	Endometrial curettage	Acute and chronic endometritis	Endometrial curettage
	Left fallopian tube	Acute and chronic salpingitis, chronic pelvic inflammatory disease	Left fallopian tube
2	Endometrial curettage (1 year prior to total abdominal hysterectomy and bilateral salpingo-oophorectomy)	Acute and chronic endometritis	Endometrial curettage
	Total abdominal hysterectomy and bilateral salpingo-oophorectomy	Acute and chronic endometritis, acute and chronic salpingitis, chronic pelvic inflammatory disease	Endometrium Right and left fallopian tubes

epithelial cells and neutrophils and in intraluminal secretions. In the epithelium, the positive staining was specific and confined to well-delineated, rounded, circumnuclear, cytoplasmic inclusions that contained finely granular particles. In the secretions and neutrophils, positive staining was seen as fine granules, suggestive of extravasated particles (Fig. 1). Tubal epithelial cells that contained pale-staining, basophilic, stippled intracytoplasmic vacuoles believed to be chlamydial organisms were identified in the corrresponding hematoxylin and eosin–stained sections (Fig. 2).

Endometrial curettings from both patients with positive staining of fallopian tubes were available for histologic review and immunoperoxidase staining. The curettings in one patient were obtained at the time of salpingectomy, and those in the second patient were from a curettage 1 year prior to abdominal hysterectomy and bilateral salpingo-oophorectomy. The endometrial specimens from both patients contained immunoperoxidase-positive intraepithelial chlamydial inclusions and granules similar to those previously described; the histologic diagnosis in both cases was acute and chronic endometritis. A severe, acute, inflammatory infiltrate was present in both endometrial specimens. Sections of the cervix from the hysterectomy specimen of the second patient were histologically unremarkable, and there was no evidence of cervicitis. The endometrium of the resected uterus contained a moderate chronic inflammatory infiltrate and was immunoperoxidase-positive for chlamydial antigens (Table I).

Chlamydial cultures. A review of the chlamydial culture records of the Department of Microbiology did not show that culturing for chlamydia had been done in any of the 70 cases analyzed.

Comment

In this series, immunoperoxidase positivity was found in only two (3%) of the 70 cases of acute salpingitis that were reviewed. This percentage of positive staining is much lower than would be expected in view of the purported role of chlamydia in salpingitis, but it is well recognized that the incidence of chlamydial infection varies geographically and depends on the population group studied.[5] Previously published studies on immunofluorescent staining for chlamydial antigens reported that the sensitivity of the technique depends upon the number of elementary, intermediate, and initial chlamydial bodies present within the cytoplasmic inclusions.[6] We would anticipate that peroxidase staining for chlamydial antigens would have a similar threshhold of sensitivity. Even though the number of cases detected was small, the immunoperoxidase technique appears to be useful in the cytologic identification and localization of chlamydia-infected epithelial cells. Virtually all of the cells which stained positively had the typical intracytoplasmic inclusions that are seen in chlamydia infections. Although similar findings were reported with immunofluorescence techniques, the immunoperoxidase technique has the advantage of useability on paraffin-embedded, stored, tissue blocks, so that cases may be studied retrospectively. In the present series, for example, we showed that the endometrial specimens from the two patients with immunoperoxidase-positive fallopian tubes were also positive for chlamydial inclusions by immunoperoxidase, including two sequential endometrial specimens 1 year apart in one patient.

In studying the localization of chlamydial antigens within the fallopian tubes, we found positive staining only within the luminal debris and tubal epithelial cells. No staining was identified in the walls of the tubes. Several authors have noted the absence of stromal infection even in cases in which an intense inflammatory response was present.[7] Possibly, this stromal inflammatory response represented an overgrowth with other organisms. Since chlamydia appears to be epithelium-specific, chlamydial cultures of the infected fallopian tubes may be facilitated by scraping or biopsying the tubal epithelium within the salpingeal lumen or sampling the epithelium after surgical resection. It is noteworthy that chlamydial culturing was not performed in a single case in this series, despite the ready accessibility of the endocervix and endometrium for sampling, and the literature documentation of the high frequency of generalized genital glandular epithelial infection by chlamydia.

In our previous studies of chlamydial immunoperoxidase staining of endocervical and endometrial specimens, we found a high degree of correlation between immunoperoxidase positivity and the severity of the inflammation. The positive cases routinely contained extensive neutrophilic infiltrates and sometimes purulent inflammation. Even though we did not find a similar association in this series of cases of acute salpingitis (all with severe acute and purulent inflammation), the immunoperoxidase technique may be useful diagnostically in identifying chlamydial infection, especially in cases in which the clinicopathologic features are suggestive, severe acute and chronic endometritis is present, and, retrospectively, chlamydial cultures have not been obtained. Because of the reportedly high incidence of chlamydial infection and its serious postinfectious sequelae, both the pathologist and the clinician should be aware of the need for chlamydial culturing.

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Chlamydia trachomatis isolation in patients with endometritis after cesarean section

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Cervical specimens for *Chlamydia* were collected from 110 patients with endometritis after cesarean section and from 52 intrapartum patients without clinical infection. The *C. trachomatis* isolation rate was not statistically different between these groups. (AM J OBSTET GYNECOL 1985;152:278-9.)

Key words: *Chlamydia,* endometritis

The role of *Chlamydia trachomatis* in postpartum endometritis is unclear because current studies are contradictory.[1, 2] With a different design, this study reports the rates of *C. trachomatis* isolation from the cervix of patients with post–cesarean section endometritis and from patients without clinical infection.

From November, 1982, to December, 1983, cervical specimens were collected from patients with endometritis after cesarean section. Samples were collected at the onset of endometritis, before use of therapeutic antibiotics (usually clindamycin plus gentamicin or aztreonam). For comparison, cervical specimens were obtained through a speculum from intrapartum patients

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Informed consent was obtained from patients, and guidelines for human experimentation of the author's institution were followed in the conduct of this research.

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before use of any antiseptic or lubricant. Comparison patients were excluded if they had received any antibiotics or had developed infection up to 3 weeks after delivery. Most patients were indigent and Mexican-American. Cervical specimens were collected with a Calgiswab (Spectrum Diagnostics, Inc., Glenwood, Illinois), placed in minimal essential media with fetal calf serum and antibiotics, and stored at − 72° C until cultured on cycloheximide-treated McCoy cells.[3] Statistical analysis was by χ^2 or Fischer's exact test, where appropriate, and by the unpaired Student t test.

Cervical samples were collected from 110 women who developed post–cesarean section endometritis and 52 intrapartum women who developed no clinical infection. The mean age of the endometritis group was 23.3 ± 5.6 years compared with 21.5 ± 4.8 years for the intrapartum women ($p < 0.05$), and the mean parity was 1.4 ± 1.6 versus 0.9 ± 1.2, respectively ($p < 0.05$). One patient in the intrapartum group was delivered abdominally. We isolated *Chlamydia* in eight (7.3%) patients with endometritis and in one (1.9%) intrapartum patient (NS). The eight women with endometritis and *Chlamydia* in the cervix responded to initial antibiotics. Isolation rates for *C. trachomatis* are similar to those found in this population. Previously we noted that two (4.3%) of 46 antepartum women and seven (3.8%) of 183 nonpregnant women attending a dysplasia clinic had cervical *Chlamydia* (J. D. Blanco, M.D., unpublished data). None of these rates was significantly different from the rate in the patients with endometritis or the intrapartum patients.

Wager et al.[1] previously reported an association between the antepartum isolation of *Chylamydia* and "late postpartum endometritis." Of 391 antepartum women, 32 (8%) had *Chlamydia* in the cervix. Puerperal infections were divided into "early postpartum fever" (occurring within 48 hours of delivery) and "late postpartum endometritis" (from 48 hours to 6 weeks post partum). Twenty-two percent (seven of 32) of the *Chlamydia*-positive patients developed "late postpartum endometritis" compared with 5% (18 of 359) of the *Chlamydia*-negative patients ($p < 0.005$). No statistically significant difference was found in the development of "early postpartum fever" (3% [one of 32] versus 7% [26 of 359]; NS).

In a similar study, Harrison et al.[2] isolated *C. trachomatis* in 8% of antepartum women tested. However, they did not find a statistically increased risk of "endometritis–postpartum fever" for these patients; 2.9% of all the study patients developed "endometritis–postpartum fever" compared with 4.1% of the patients with *C. trachomatis* in the cervix (NS). The discordant results of the studies of Wager et al. and Harrison et al. may be explained by different definitions of clinical infection, patient populations, risk factors for puerperal infection, or the confounding effect of other microorganisms.

The experimental design of the present study was different. We compared the rate of cervical chlamydial infection in patients with endometritis and no clinical infection and found no statistically significant difference in rates of cervical chlamydial isolation. These data do not support a role for *C. trachomatis* in early post–cesarean section endometritis. Since all of our patients with endometritis developed clinical infection within 3 days after delivery, we cannot comment on the possible association of *Chlamydia* and "late endometritis."

Although there were statistically significant differences in mean age and parity between the endometritis and comparison groups, these absolute differences were small and probably not clinically meaningful. There are age-related differences in the isolation of cervical *Chlamydia*, but the association is toward higher isolation rates in the younger age groups. Since, in this study, the comparison group was younger than the endometritis group, the age difference, if it has any influence, might be expected to increase the isolation rate in the comparison group.

By design, the rate of abdominal delivery was markedly different between the patients with endometritis and the intrapartum patients. The ideal comparison group would have been uninfected patients who had not received antibiotics after an abdominal delivery. With the high rate of endometritis after cesarean section and the widespread use of prophylactic antibiotics, there were few such patients available for study. Therefore we compared the rate of *C. trachomatis* isolation in the group with endometritis with rates in the overall population, regardless of type of delivery. If cervical *C. trachomatis* resulted in early postpartum endometritis, the rate in the patients with infections should be higher than the rate in the overall population. There is no reason to believe that the route of delivery would alter the rate of *Chlamydia* isolation or that patients with *C. trachomatis* would be more likely to have a cesarean delivery.

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Prevalence and manifestations of endometritis among women with cervicitis

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Thirty-five women referred from a clinic treating sexually transmitted diseases, because of suspected cervicitis, were studied for the presence of endometritis by transcervical endometrial biopsies and cervical and endometrial cultures. Fourteen (40%) of the patients had histologic evidence of endometritis. Findings that significantly correlated with endometritis included a history of intermenstrual vaginal bleeding, the presence of *Chlamydia trachomatis, Neisseria gonorrhoeae,* or *Streptococcus agalactiae* in the cervix, and the presence of serum antibodies to *C. trachomatis* or to *Mycoplasma hominis.* (AM J OBSTET GYNECOL 1985;152:280-6.)

Key words: Endometritis, cervicitis, chlamydia, gonorrhea, plasma cell, salpingitis

It is commonly accepted that acute nontuberculous salpingitis develops when pathogenic microorganisms ascend along the endometrial mucosal surface from an infected cervix to the fallopian tubes.[1] Thus endometritis may represent a state in the continuum between cervicitis and salpingitis. Despite the possible importance of endometritis as an intermediate stage of infection, the presence of endometritis has not been extensively studied either among women with cervicitis or among women with salpingitis, and the microbiologic features of endometritis remain undefined. In this study, we examined the prevalence, histopathologic characteristics, and microbiologic features of endometritis associated with mucopurulent cervicitis.

Material and methods

Study population. Consecutive women with suspected cervicitis who spontaneously attended a clinic treating sexually transmitted diseases were eligible for the study. These women were from a larger group of women with cervicitis who have been previously described.[2] Clinicians were asked not to refer women who were under 16 years of age, had taken antibiotics in the prior month, were wearing an intrauterine contraceptive device, were suspected on the initial examination of having pelvic inflammatory disease (presence of moderate to severe adnexal tenderness or a temperature of ≥38° C). Women with these findings were excluded. Thirty-seven women who agreed to participate in the study gave written informed consent. Endometrial tissue was obtained for histologic study in 35 women who are included in this report.

Patient evaluation. A standardized interview concerning the menstrual history, contraceptive method, sexual history, and a prior history of sexually transmitted diseases was obtained from all women. All women underwent a standard gynecologic examination. The presence of mucopurulent endocervical discharge was confirmed by visualization of yellow endocervical mucopus on a white swab. The severity of inflammation of the endocervical epithelium was assessed by separately scoring the degree of induced mucosal bleeding as well as erythema and edema of the zone of ectopy as described.[2] The presence of cervical motion or uterine or adnexal tenderness was determined by a bimanual examination. An endometritis severity score was derived by adding one point for each of the following findings: intermenstrual bleeding, lower abdominal pain, cervical motion tenderness, uterine tenderness, and adnexal tenderness. Quantitation of leukocytes in endocervical secretions was performed as previously described in detail.[2]

Definition of mucopurulent cervicitis. As previously described,[2] a diagnosis of mucopurulent cervicitis was established on the basis of the presence of either a

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yellow mucopurulent endocervical discharge or ≥10 polymorphonuclear leukocytes per 1000× microscopic field in cervical mucus on a satisfactory smear.

Laboratory methods and collection of specimens. An unlubricated speculum was inserted into the vagina and the cervix was exposed. Vaginal pH was measured directly from the posterior vaginal fornix with pH indicator paper. A sterile filter paper strip (5 by 20 mm) was inserted into the endocervical canal and allowed to become saturated with fluid from cervical mucus. This was done carefully to avoid bleeding from the endocervix during the procedure. The filter paper strip was placed in 0.2 ml of phosphate-buffered saline and assayed for antibody to *Chlamydia trachomatis.* A type III calcium alginate swab (Inolex Division, Glenwood, Illinois) was used to obtain cervical material for the culture of *C. trachomatis* by rotating the swab several times in the endocervical canal. Subsequent successive endocervical specimens were obtained with cotton-tipped swabs for the isolation of *Neisseria gonorrhoeae, Mycoplasma hominis, Ureaplasma urealyticum, Gardnerella vaginalis, Streptococcus agalactiae,* herpes simplex virus, and cytomegalovirus. Three milliliters of sterile distilled water was then pipetted into the posterior vaginal fornix, and a cotton swab was used to mix the remaining vaginal secretions into the water. The mixture was then removed from the vagina with a pipette, and a portion was mixed with saline solution and 10% potassium hydroxide and microscopically examined to identify clue cells, *Trichomonas vaginalis,* fungal elements, and amine order. The remainder was injected into a tube that was tightly capped and frozen at −20° C until biochemical studies were performed. A clinical diagnosis of bacterial vaginosis was made on the basis of the presence of three of four of the following characteristics: a pH ≥4.7, abnormal homogeneous discharge adherent to the vaginal walls, fishy odor when mixed with 10% potassium hydroxide, and clue cells when they represented ≥20% of all vaginal epithelial cells on wet mount examination.

Specimens were obtained for culture from all women by transcervical endometrial aspiration. The cervix was first wiped carefully three times with povidone-iodine swabs. A fourth cotton-tipped swab soaked in alcohol-iodine was placed in the endocervical canal for 2 minutes. A sterile disposable Pro-Ception fertility cannula (Milex Co., Chicago, Illinois) was inserted into the endocervical canal through the internal os. When the catheter was properly placed, the stylet was removed, and a disposable cul-de-sac aspiration catheter (C. R. Bard, Inc., N.J.) was inserted through the cannula beyond the internal os until it was felt to touch the uterine fundus. A 5 ml syringe was affixed to the catheter and moderate suction was applied momentarily. After endometrial material was removed by suction, the catheter was removed while the outer cannula was still in place. The aspirate in the catheter was then immediately inoculated onto or into culture media for isolation of the following microorganisms: *C. trachomatis, N. gonorrhoeae, M. hominis, U. urealyticum,* herpes simplex virus, cytomegalovirus, and other facultative and anaerobic bacteria.

Endometrial biopsy and histopathologic studies. After the endometrial culture aspiration was performed, a single-strip endometrial biopsy specimen was retrieved transcervically from 35 of 37 women with a sterile disposable endometrial suction curette (Tis-U-Trap, Milex Co.) equipped with a metallic tip 3 mm in diameter. No anesthesia was required for this procedure. The biopsy specimens were fixed in formalin and stained with hematoxylin-eosin and with methyl green–pyronine for the demonstration of plasma cells. The histopathologic examination of the biopsy specimens was performed by a pathologist (N. K.) in a blind fashion as to the clinical and microbiologic findings. The number of plasma cells was quantitated in six sections prepared from progressively deeper levels through the same tissue block. The diagnosis of endometritis was based on the presence of at least 10 plasma cells in any of the six tissue sections. If <10 plasma cells were seen in a section and the area of the section was less than three times the area of a 400× microscopic field, the specimen was considered inadequate. For comparison, we studied the presence or absence of plasma cells in endometrial biopsies obtained from 35 consecutive patients who underwent evaluation for infertility during the same period of time. These patients ranged in age from 25 to 39 (mean 32).

Microbiologic studies. The isolation of *C. trachomatis, N. gonorrhoeae,* and herpes simplex virus was performed as previously described.[2] Specimens were inoculated on A7 agar plates[3] and into broth media for isolation of *M. hominis* and *U. urealyticum.*[4] Broth showing evidence of growth was subcultured onto A7 agar medium for confirmation. Colonies were identified by typical morphologic features. Specimens were inoculated on selective differential agar medium (HBT) for the isolation of *G. vaginalis.* Colonies showing β-hemolysis were further identified as *G. vaginalis* as previously described.[5] Specimens were inoculated into Todd-Hewitt broth containing 5% sheep blood and 5 μg/ml gentamicin and 15 μg/ml nalidixic acid for the isolation of *S. agalactiae* (group B *Streptococcus*). *S. agalactiae* was identified on the basis of β-hemolytic reaction and CAMP reaction on sheep blood agar. Endometrial specimens were inoculated into Port-A-Cul transport tubes (BBL, Cockeysville, Maryland) and were routinely cultured in anaerobic chambers for isolation of other facultative and anaerobic bacteria, which were identified as previously described.[6] Cervicovaginal specimens

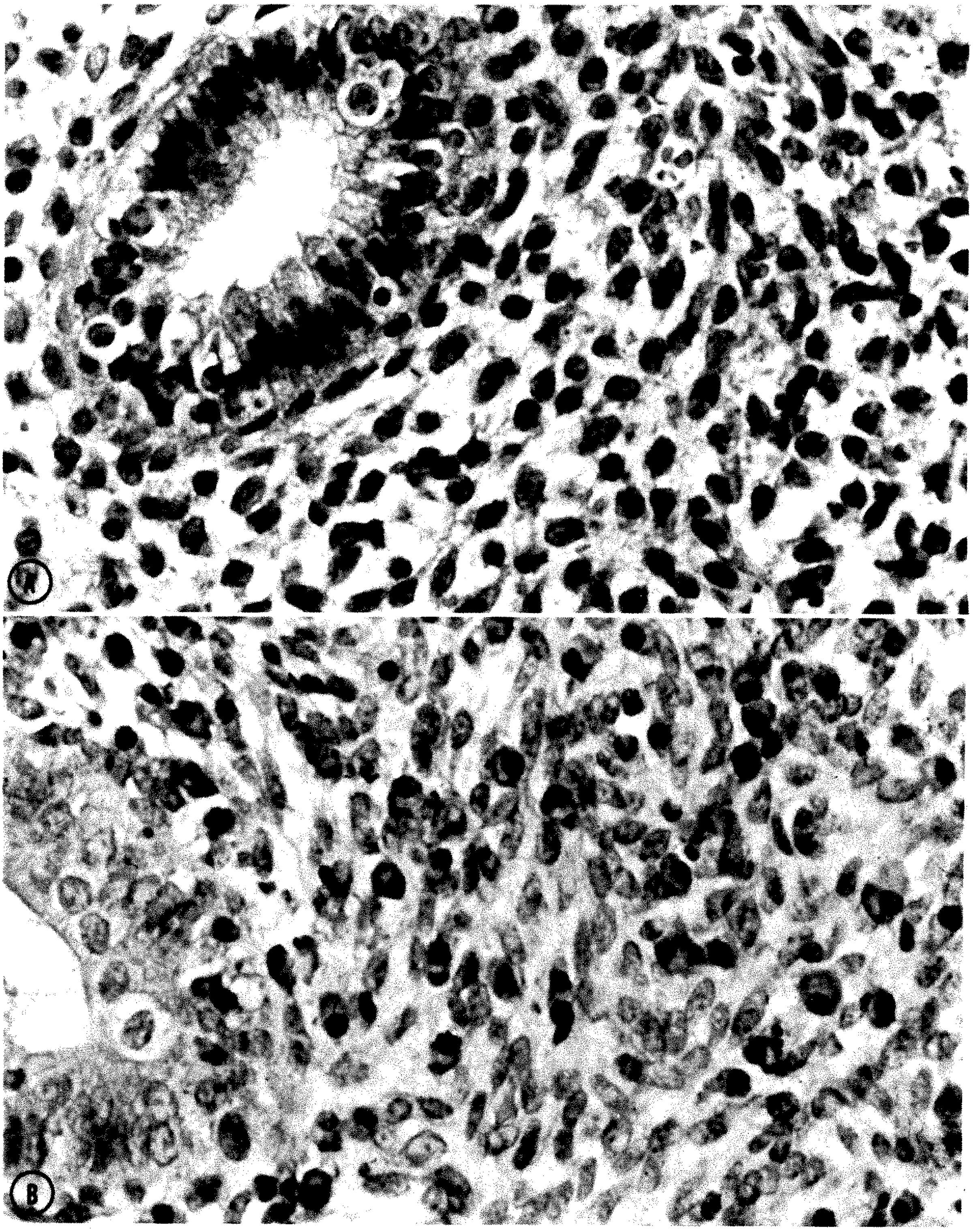

Fig. 1. Biopsy specimens from normal endometrium *(A)* and plasma cell endometritis *(B)*. (Methyl green–pyronine stain; × 1000.)

were inoculated into Diamond's medium for isolation of motile trichomonads and onto Sabouraud's agar plates for the isolation of *Candida albicans* or other yeasts, which were identified by standard method.

Biochemical studies. Vaginal wash samples were analyzed for organic acids by gas-liquid chromatography as described by Spiegel et al.[6] and for abnormal diamines (putrescine and cadaverine) by a thin-layer

Table I. Clinical and laboratory findings stratified by the presence of plasma cell endometritis

	Endometritis present (n = 14)		*Endometritis not present (n = 21)*	
	No.	*%*	*No.*	*%*
Birth control method				
Oral contraceptives	10	71	14	67
Barrier method	0	—	3	14
Other methods	2	14	1	5
None	1	7	2	10
Symptoms				
Intermenstrual bleeding	9	64*	5	24
Postcoital bleeding	6	43	4	19
Low abdominal pain	9	64	15	71
Physical findings				
Cervical motion tenderness	8	57	8	38
Uterine tenderness	8	57†	7	33
Adnexal tenderness	2	14	3	14
Mean cervicitis severity score	6.0 ± 2.1		4.4 ± 2.5	
Mean area of cervical ectopy (%)	38.5 ± 29.5		31.8 ± 25.9	
Mean number of PMNs on cervical Gram stain	29.8 ± 15.8		34.7 ± 17.3	
Findings of bacterial vaginosis				
Clinical bacterial vaginosis	4/12	33	5/20	25
Presence of abnormal S/L ratio‡ in vaginal washing	4/12	33	4/16	25
Presence of abnormal amines§ in vaginal fluid	5/12	42	9/15	60
Hematologic findings				
Elevated ESR‖ and/or peripheral WBC¶ count	5	36†	2	10

PMN = Polymorphonuclear leukocytes; S/L ratio = succinate/lactate ratio.
*p = 0.02.
†p = 0.06.
‡Succinate/lactate ratio measured by gas-liquid chromatography.
§Putrescine or cadaverine measured by thin-layer chromatography.
‖Erythrocyte sedimentation rate ≥20 mm/hour.
¶White blood cell count ≥10,000/mm^3.

chromatography method described by Chen et al.[7] Results of gas-liquid chromatographic analysis were defined as abnormal when the succinate/lactate peak ratio was ≥0.4.

Hematologic studies. Ten milliliters of blood was collected at the initial visit for determination of the white blood cell count and the erythrocyte sedimentation rate.

Serum and secretion antibody determination. Serum samples were tested by the microimmunofluorescence technique for IgG and IgM antibodies to all *C. trachomatis* elementary body serovars.[8] Cervical secretions were similarly tested for secretory IgA antibodies to *C. trachomatis*.

Serum IgG antibodies to *M. hominis* were determined with a four-layer modification of enzyme immunoassay with *M. hominis* type strain H-34 (ATCC-15056) used as antigen, as described.[9] Levels of antibody activity were expressed in arbitrary enzyme immunoassay units.

Statistical methods. We used the χ^2 test, Mantel-Haenszel test, or Student's *t* test, where appropriate, for statistical comparisons.

Results

Prevalence of endometritis. Thirty of the 35 women had gross mucopurulent endocervical discharge, and four of the remaining five had ≥10 polymorphonuclear leukocytes per 1000× microscopic field in the cervical mucus. Histopathologic evidence of plasma cell endometritis as presented in Fig. 1 was found in 14 (40%) of the 35 women, including 14 (47%) of 30 women with gross endocervical mucopus and none of five women without endocervical mucopus (p = 0.06). There was no correlation between the presence of plasma cell endometritis and the day of the menstrual cycle when the endometrial biopsy specimen was obtained or with the method of contraception practiced.

Plasma cells were seen in only one (3%) of the endometrial biopsy specimens obtained from the 35 women who underwent evaluation for infertility.

Correlation of clinical and laboratory findings

Table II. Correlation of the clinical endometritis score with the number of plasma cells present on endometrial biopsy

*No. of plasma cells**	*Clinical endometritis score**		
	0	*1-3*	*>3*
≤25	5	19	4
26-49	0	1	0
≥50	0	2	4

$\chi^2 = 8.12$; $p < 0.02$.

*See material and methods.

with the presence of endometritis. As shown in Table I, abnormal intermenstrual bleeding had occurred among nine (64%) of 14 women with plasma cell endometritis and five (24%) of 21 women without it ($p = 0.02$). Symptoms of low abdominal pain were common in both groups. However, uterine tenderness was found in eight (57%) of 14 patients with endometritis and seven (33%) of 21 patients without it ($p = 0.06$). Cervical motion tenderness was also slightly more common in patients with histopathologic evidence of endometritis (57%) than among those without histopathologic endometritis (35%) (NS).

The presence of bacterial vaginosis (nonspecific vaginitis) as defined by clinical criteria or by biochemical criteria (a succinate/lactate ratio of ≥0.4 or an abnormal concentration of putrescine or cadaverine in the vaginal fluid) did not correlate with the presence of endometritis (Table I).

There was a significant correlation of the clinical endometritis score with the number of plasma cells seen on endometrial biopsy. A total score ≥3 was present among five (18%) of 28 women who had <25 plasma cells and among four (57%) of seven women who had ≥26 plasma cells ($p < 0.02$, Table II). An increased erythrocyte sedimentation rate or white blood cell count was present in five (36%) women with endometritis and in two (10%) women without it ($p = 0.06$).

Correlation of endometritis with the isolation of microbial agents from the cervix. Microorganisms that were significantly more often isolated from the cervix in women who had plasma cell endometritis than from the cervix in those women who did not have it (Table III) included *C. trachomatis* (86% versus 48%, $p = 0.03$), *N. gonorrhoeae* (21% versus 0%, $p = 0.03$), and *S. agalactiae* (23% versus 0%, $p = 0.04$). However, the three women from whom *S. agalactiae* was isolated also had *C. trachomatis* infection.

Correlation of endometritis with the microbial agents isolated from the endometrium. None of the microorganisms isolated from the transcervical aspirate of the endometrium was significantly associated with the presence of plasma cell endometritis (Table IV).

Correlation of endometritis with the serum and cervical secretion antibodies to *C. trachomatis* and serum antibodies to *M. hominis*. Microimmunofluorescence antibodies to *C. trachomatis* were detected among all 13 women with endometritis and 14 (74%) of 19 women without it ($p = 0.04$, Table III). High titers (≥1:128) occurred in five (38%) of 13 cases with endometritis and in four (25%) of 16 cases without it (NS). The prevalence of secretory IgA antibodies in cervical secretions did not differ between the two groups.

There was a striking correlation between endometritis and the prevalence ($p < 0.05$) and level ($p < 0.01$) of serum antibody to *M. hominis*. There was no correlation between the presence of serum microimmunofluorescence antibodies to *C. trachomatis* and the presence of serum enzyme immunoassay antibodies to *M. hominis*.

Comment

In retrospective studies of women undergoing endometrial biopsy for irregular vaginal bleeding or other reasons, plasma cell endometritis has been observed in 3% to 10% of cases.[10,11] However, little is known of the etiology of such cases of nontuberculosis endometritis; cytomegalovirus, herpes simplex virus, and *C. trachomatis* have been implicated in previously studied patients.[12-14]

In this study, histopathologic evidence of plasma cell endometritis, as we defined it, was found in 14 (40%) of 35 consecutively studied female patients from a clinic treating sexually transmitted diseases, referred for mucopurulent cervicitis, including 14 (58%) of 24 with chlamydial and/or gonococcal infection. Plasma cell endometritis was significantly correlated with isolation of *C. trachomatis*, *N. gonorrhoeae*, and *S. agalactiae* from the cervix, with the presence of serum antibody to *C. trachomatis*, and with the presence and level of serum antibody to *M. hominis*. Serum antibodies to *C. trachomatis* and *M. hominis* have also previously been correlated with salpingitis.[15] Studies of larger numbers of patients would be useful to permit a multivariate analysis of the relationship of plasma cell endometritis to each of these organisms individually, since co-infections were common in this study.

Plasma cell endometritis was not correlated with isolation of microorganisms from the endometrium itself. There are several possible explanations. Endometritis may be a patchy lesion, and single-strip biopsy may not always sample inflamed tissue. The iodine preparation of the cervix may not have prevented the introduction of cervical organisms into the endometrial aspirated specimens. Alternatively, iodine preparation of the cervix may have led to introduction of iodine into the cervix during aspiration, interfering with recovery of organisms from the aspirates. Blood in the aspirates

Table III. Correlation of plasma cell endometritis with the isolation of microorganisms from the cervix and the presence of antibodies to *C. trachomatis* and *M. hominis*

	Endometritis present (n = 14)		*Endometritis not present (n = 21)*	
	No. total	*%*	*No. total*	*%*
Isolated organism				
C. trachomatis	12	86*	10	48
N. gonorrhoeae	3	21*	0/19	—
M. hominis	7	50	7	33
U. urealyticum	12	86	17	81
G. vaginalis	14	100	18/20	90
S. agalactiae	3/13	23*	0/19	—
HSV	1/13	8	1	5
CMV	3/13	23	1	5
Micro-IF antibodies to *C. trachomatis*				
Serum antibody ≥1:8	13/13	100*	14/19	74
Serum IgA antibody in cervical secretions	6/13	46	7/19	37
EIA antibodies to *M. hominis*				
Serum IgG antibody level ≥50 EIU	7/12	58*	2/14	14
Mean IgG antibody level ± SD	45.1 ± 33.7†		17.1 ± 21.7	

HSV = Herpes simplex virus; CMV = cytomegalovirus; micro-IF = microimmunofluorescence; EIA = enzyme immunoassay; EIU = enzyme immunoassay units.

*$p < 0.05$.

†$p < 0.01$.

may also have had microbicidal activity. The number of viable organisms present in the endometrium may be lower than the number present in the cervix or vagina, perhaps below the threshold of detection in some patients.

The histopathologic criteria we used for definition of plasma cell endometritis were similar to previously described pathologic definitions of endometritis.[10, 11] The validity of our criteria was supported by the correlation of plasma cell endometritis with characteristic clinical manifestations of endometritis, such as intermenstrual bleeding, uterine tenderness, and elevated erythrocyte sedimentation rate and/or peripheral white blood cell count, as well as with the isolation of pathogens from the cervix or vagina and with serologic evidence of infection. Furthermore, the severity of endometritis by histologic criteria was correlated with the clinical severity score. Although we did not obtain endometrial biopsy specimens from a matched control group of patients without cervicitis attending the same clinic, it was of importance that plasma cells were seen in only one of the endometrial biopsy specimens retrieved from 35 patients undergoing infertility evaluation, suggesting that plasma cells are not normally found in the endometrium by the methods we used in this study.

C. trachomatis and *N. gonorrhoeae* are the principal causes of acute salpingitis, while *M. hominis* and *S. agalactiae* have also been implicated. The spread of *N. gonorrhoeae* and *C. trachomatis* to the fallopian tubes is thought to occur by intraluminal spread via the endometrium. The prevalence of salpingitis among those with endometritis was not defined in the present study. Does gonococcal or chlamydial endometritis occur as a discrete stage preceding development of salpingitis, or

Table IV. Correlation of endometritis with the isolation of microorganisms from the endometrium

	Endometritis present (n = 14)		*Endometritis not present (n = 21)*	
	No. total	*%*	*No. total*	*%*
*C. trachomatis**	2	14	3	14
N. gonorrhoeae	1	7	1	5
M. hominis	3/13	23	5	24
U. urealyticum	3/13	23	5	24
Herpes simplex virus†	2	14	0	—
Cytomegalovirus‡	2	14	0	—
S. agalactiae§	1/8	13	0	—
Other facultative bacteria‖	2/8	25	3/12	25
Anaerobic bacteria‖	0/8	—	1/12	8

*Isolated from the cervix in all women with positive endometrial cultures.

†Also isolated from the cervix in one of two women who had positive endometrial cultures.

‡Also isolated from the cervix in one of two women who had positive endometrial cultures.

§Not isolated from the cervix in the woman who had a positive endometrial culture.

‖Port-A-Cul culture yielded growth of one or more of the following bacteria: *Staphylococcus epidermidis*, nonhemolytic *Streptococcus*, α-hemolytic *Streptococcus*, *Peptococcus asaccharolyticus*, *Escherichia coli*.

do endometritis and salpingitis tend to evolve simultaneously? Since endometritis was present in the majority (58%) of women with chlamydial or gonococcal endocervicitis, might it also be true that endosalpingitis was present in more women with chlamydial or gonococcal endometritis? Further studies are needed to assess the prevalence of salpingitis among women presenting with cervicitis and endometritis as in the present study, as well as the endometrial pathologic conditions among patients presenting with acute salpingitis.

In their classical study, Jacobson and Weström[16] found laparoscopic evidence of salpingitis among 65% of 814 women with a clinical diagnosis of salpingitis. Twenty-three percent of the women undergoing laparoscopy had normal-appearing fallopian tubes, although the prevalence of lower genital tract inflammation, gonococcal infection of the cervix, fever, increased white blood cell count, and increased sedimentation rates was similar to that of women with laparoscopically visualized salpingitis. It is possible that some of the women with normal-appearing fallopian tubes had endometritis and mild endosalpingitis that could not be readily recognized through the laparoscope.

The frequency of infertility following endometritis is unknown. Women in the study of Jacobson and Weström whose fallopian tubes appeared normal at laparoscopy subsequently had normal fertility. On the other hand, only about half of women with infertility due to tubal occlusion previously had a recognized episode of salpingitis. It is possible that mucopurulent cervicitis and endometritis may be the only signs of pelvic inflammatory disease in a large proportion of women with chlamydial or gonococcal infection who will develop tubal scarring. In fact, these may be the most reversible manifestations of pelvic inflammatory disease and therefore the most important to recognize and treat before irreversible tubal occlusion has developed.

In conclusion, endometrial biopsy is a useful technique for establishing the presence or absence of endometritis, and it deserves further evaluation in conjunction with laparoscopy in future studies of the diagnosis and pathogenesis of pelvic inflammatory disease. It appears particularly useful for confirming the diagnosis of endometritis among women with mucopurulent cervicitis who have additional symptoms, signs, or laboratory findings suggestive of endometritis. Prompt antimicrobial therapy administered to such women with mucopurulent cervicitis and/or endometritis may prevent subsequent or simultaneous salpingitis and subsequent infertility.

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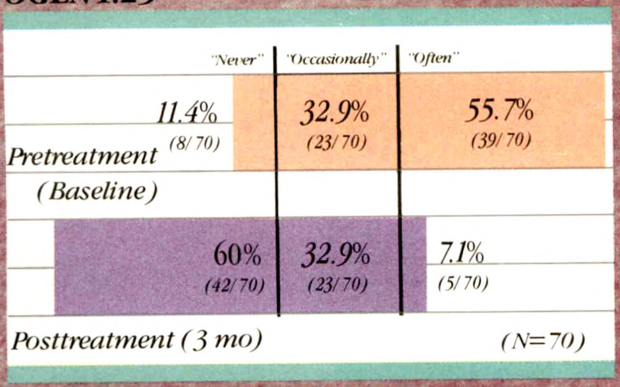

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Reference:
1. Wren BG, Brown LB, Routledge DA: Differential clinical response to oestrogens after menopause. *Med J Aust* 2:329-332, 1982.

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ESTROPIPATE TABLETS, USP

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WARNING:

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. OGEN SHOULD NOT BE USED DURING PREGNANCY.

According to some investigators, the use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. Studies have reported that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] In one of these studies, this risk was estimated as not greater than 4 per 1000 exposures.[7] Furthermore, there are reports that a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these reported changes are histologically benign, the investigators have not determined whether they are precursors of adenocarcinoma.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies in the offspring, including heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. OGEN has not been studied for these uses, and therefore should not be used during pregnancy. There is no evidence from well controlled studies that progestogens are effective for these uses.

If OGEN (estropipate tablets) is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the question of continuation of the pregnancy should be addressed.

INDICATIONS

OGEN (estropipate tablets) is indicated for the treatment of estrogen deficiency associated with:

1. Moderate to severe *vasomotor* symptoms of menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.

OGEN (ESTROPIPATE TABLETS) HAS NOT BEEN TESTED FOR EFFICACY FOR ANY PURPOSE DURING PREGNANCY. SINCE ITS EFFECT UPON THE FETUS IS UNKNOWN, IT CANNOT BE RECOMMENDED FOR ANY CONDITION DURING PREGNANCY (SEE BOXED WARNING).

CONTRAINDICATIONS

OGEN should not be used in women with any of the following conditions:

1. Known or suspected cancer of the breast.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (See Boxed Warning).
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use.

WARNINGS

1. *Induction of malignant neoplasms.* Long-term continuous administration of natural and synthetic estrogens in certain animal species has been reported by some investigators to increase the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning).

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent long-term followup of a single physician's practice has raised this possibility.[18] Therefore, caution should be exercised when administering estrogens to women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. Careful breast examinations should be performed periodically.

2. *Gall bladder disease.* A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens,[17] similar to the 2-fold increase previously noted in users of oral contraceptives.[19,22] In the case of oral contraceptives, the increased risk appeared after two years of use.[22]

3. *Effects similar to those caused by estrogen-progestogen oral contraceptives.* There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat postpartum breast engorgement would be more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in women receiving estrogens for postpartum breast engorgement.[20,21]

a. *Thromboembolic disease.* It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[22-29] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.[30,31] An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives.[32,33] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism; it should also be discontinued during periods of prolonged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found[17,34] this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk. Therefore estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

b. *Hepatic adenoma.* Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[36-38] Although benign, and rare, these may rupture and cause death through intraabdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[37] The relationship of this malignancy to these drugs is not known at this time.

c. *Elevated blood pressure.* Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with use of estrogens in the menopause[39] and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. *Glucose tolerance.* A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

4. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS

A. General Precautions.

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

2. Fluid retention — Estrogens may cause some degree of fluid retention. Therefore, patients with conditions such as epilepsy, migraine, and cardiac or renal dysfunction, which might be influenced by this factor, require careful observation.

3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression.[22] Although it is not clear whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size during estrogen use.

6. The pathologist should be advised of the patient's use of estrogen therapy when relevant specimens are submitted.

7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen.

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

B. Information for the Patient. See text of Patient Package Insert which appears after PHYSICIAN REFERENCES.

C. OGEN (estropipate tablets) cannott be recommended for use during pregnancy. See Contraindications and Boxed Warning.

D. Nursing Mothers. Estrogens have been reported to be excreted in human breast milk.

ADVERSE REACTIONS

(See Warnings regarding reports of possible induction of neoplasia, unknown effects upon the fetus, increased incidence of gall bladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

1. *Genitourinary system.*
Breakthrough bleeding, spotting, change in menstrual flow.
Dysmenorrhea.
Premenstrual-like syndrome.
Amenorrhea during and after treatment.
Increase in size of uterine fibromyomata.
Vaginal candidiasis.
Change in cervical eversion and in degree of cervical secretion.
Cystitis-like syndrome.

2. *Breast.*
Tenderness, enlargement, secretion.

3. *Gastrointestinal.*
Nausea, vomiting.
Abdominal cramps, bloating.
Cholestatic jaundice.

4. *Skin.*
Chloasma or melasma which may persist when drug is discontinued.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Loss of scalp hair.
Hirsutism.

5. *Eyes.*
Steepening of corneal curvature.
Intolerance to contact lenses.

6. *CNS.*
Headache, migraine, dizziness.
Mental depression.
Chorea.

7. *Miscellaneous.*
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria.
Edema.
Changes in libido.

ACUTE OVERDOSAGE

Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that serious ill effects do not occur. Overdosage of estrogen may cause nausea and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

1. *Given cyclically for short-term use:*

For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., 3 weeks on and 1 week off).

Attempts to discontinue or taper medication should be made at 3 to 6 month intervals.

The usual dosage range is one OGEN .625 (estropipate) Tablet to one OGEN 5 Tablet per day.

2. *Given cyclically:*

Female hypogonadism. Female castration. Primary ovarian failure. The lowest dose that will control symptoms should be chosen. A daily dose of one OGEN 1.25 Tablet to three OGEN 2.5 Tablets may be given for the first three weeks of a theoretical cycle, followed by a rest period of eight to ten days. The same schedule is repeated if bleeding does not occur by the end of the rest period. The duration of cyclic estrogen therapy necessary to produce withdrawal bleeding will vary according to the responsiveness of the endometrium. If satisfactory withdrawal bleeding does not occur, an oral progestogen may be given in addition to estrogen during the third week of the cycle.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

OGEN (estropipate tablets, USP) is supplied as OGEN .625 (0.75 mg estropipate), yellow tablets, **NDC** 0074-3943-04; OGEN 1.25 (1.5 mg estropipate), peach-colored tablets, **NDC** 0074-3946-04; OGEN 2.5 (3 mg estropipate), blue tablets, **NDC** 0074-3951-04; and OGEN 5 (6 mg estropipate), light green tablets, **NDC** 0074-3958-13. Tablets of all four dosage levels are standardized to provide uniform estrone activity and are grooved (Divide-Tab®) to provide dosage flexibility. All tablet sizes of OGEN are available in bottles of 100.

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AJS-044

Actinomyces and the intrauterine contraceptive device: Aspects of the fluorescent antibody stain

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Using fluorescein-conjugated globulins specific for *Actinomyces israelii* and *Arachnia propionica*, we observed large dispersed actinomycete populations in vaginal smears of several asymptomatic women. Mycelial granules, commonly revealed by the Papanicolaou stain, were not seen. These observations are discussed in regard to the threat of infection and sensitivity of the fluorescent stain. (AM J OBSTET GYNECOL 1985;152:287-90.)

Key words: *Actinomyces israelii, Arachnia propionica,* intrauterine contraceptive device, fluorescent antibody stain, genital actinomycetes

Using the fluorescent antibody stain, we described the presence of *Actinomyces israelii, Actinomyces naeslundii,* and *Arachnia propionica* in the cervicovaginal smears of asymptomatic women who had or had not used an intrauterine contraceptive device.[1, 2] Subsequently, we have observed large disseminated populations of actinomycetes in the vaginal smears of several asymptomatic women. We address ourselves here to these observations and to several recent publications which have specific relevant points of interest.

Material and methods

Slides were prepared from 11 asymptomatic women who wore an intrauterine contraceptive device, and who had no evidence of pelvic inflammatory disease.[1] They were examined for the presence of *A. israelii* and *A. propionica*, only. The slides were heat-fixed, digested with pepsin, and stained with the specific fluorescein-conjugated globulins as described previously,[1] but the rhodamine counterstain was not used. The reagents were obtained from the Biological Products Program, Center for Infectious Diseases, Atlanta, Georgia.

Results and comment

Recently, in his reply to Bhardwaj, Sweet[3] stated that, "Controversy exists relative to management of asymptomatic women with an intrauterine contraceptive device in place and *Actinomyces* noted on Papanicolaou smear. Presently, we remove the intrauterine contraceptive device from such women without antibiotic coverage and reinsert an intrauterine contraceptive device when the Papanicolaou smear is negative for *Actinomyces.*" In Fig. 1, *A*, we show a typical mycelial granule, Papanicolaou stained as originally described by Gupta et al.,[4] whereas in Fig. 1, *B*, we show a second granule stained with the specific fluorescent antibody–conjugate for *A. israelii;* both slides were prepared from asymptomatic patients who wore an intrauterine contraceptive device. In Fig. 2, we present several fields from slides stained with fluorescent antibody–conjugates taken from cervicovaginal smears of an asymptomatic patient who was using an intrauterine contraceptive device; these show the presence of free and cell-associated elements of *A. israelii* microcolonies and the cells and various filamentous forms of *A. propionica.* Large mycelial granules such as those of Fig. 1, *B*, were not seen. It is obvious that, although the Papanicolaou stain can be used with relative high efficiency for the identification of actinomycetic granules,[5] it does not reveal small groups or individual bacterial cells which, in contrast, are readily seen with the fluorescent antibody stain (Fig. 1, *B*). In some instances, the so-called actinomycetic filaments stained by the Papanicolaou procedure are actually nonactinomycetic bacterial chains. These would not be stained by the specific fluorescent antibody–conjugates.[1, 10] When the mycelial granules of Fig. 1 are compared to the cervicovaginal smears depicted in Fig. 2, in which there were no granules but numerous microcolonies or clusters of a few cells dispersed throughout all the slides, we see that two quite different kinds of actinomycete populations are present. The large actinomycete masses shown by the Papanicolaou stain differ little from similar mycelial granules described below, which colonize tonsillar crypts or the lacrimal canal. On the other hand, the disseminated

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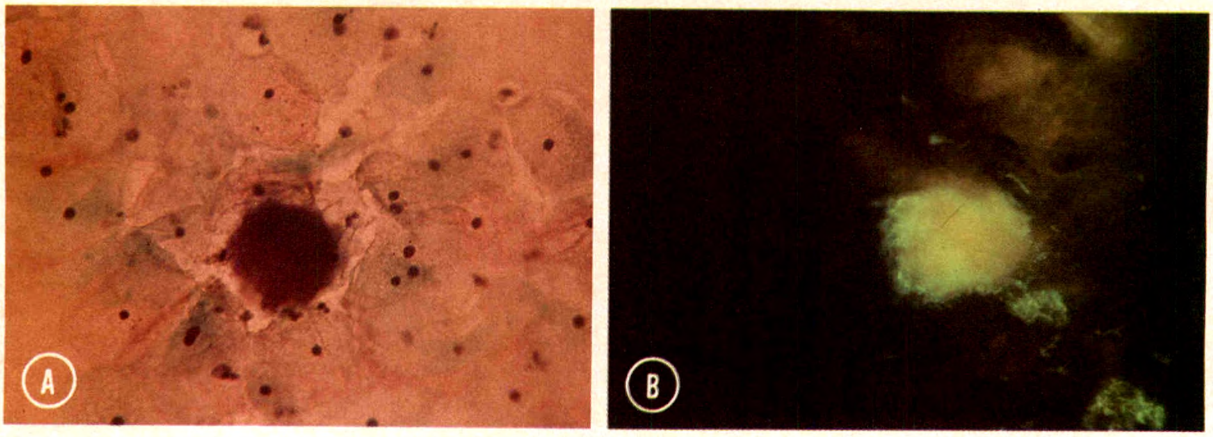

Fig. 1. Actinomyces granules resulting from surface colonization in women with an intrauterine contraceptive device. *A,* Granule stained by the Papanicolaou stain. (×400.) *B,* Granule stained by fluorescein-conjugated antibody specific for *A. israelii,* serotypes 1 and 2. (×400.)

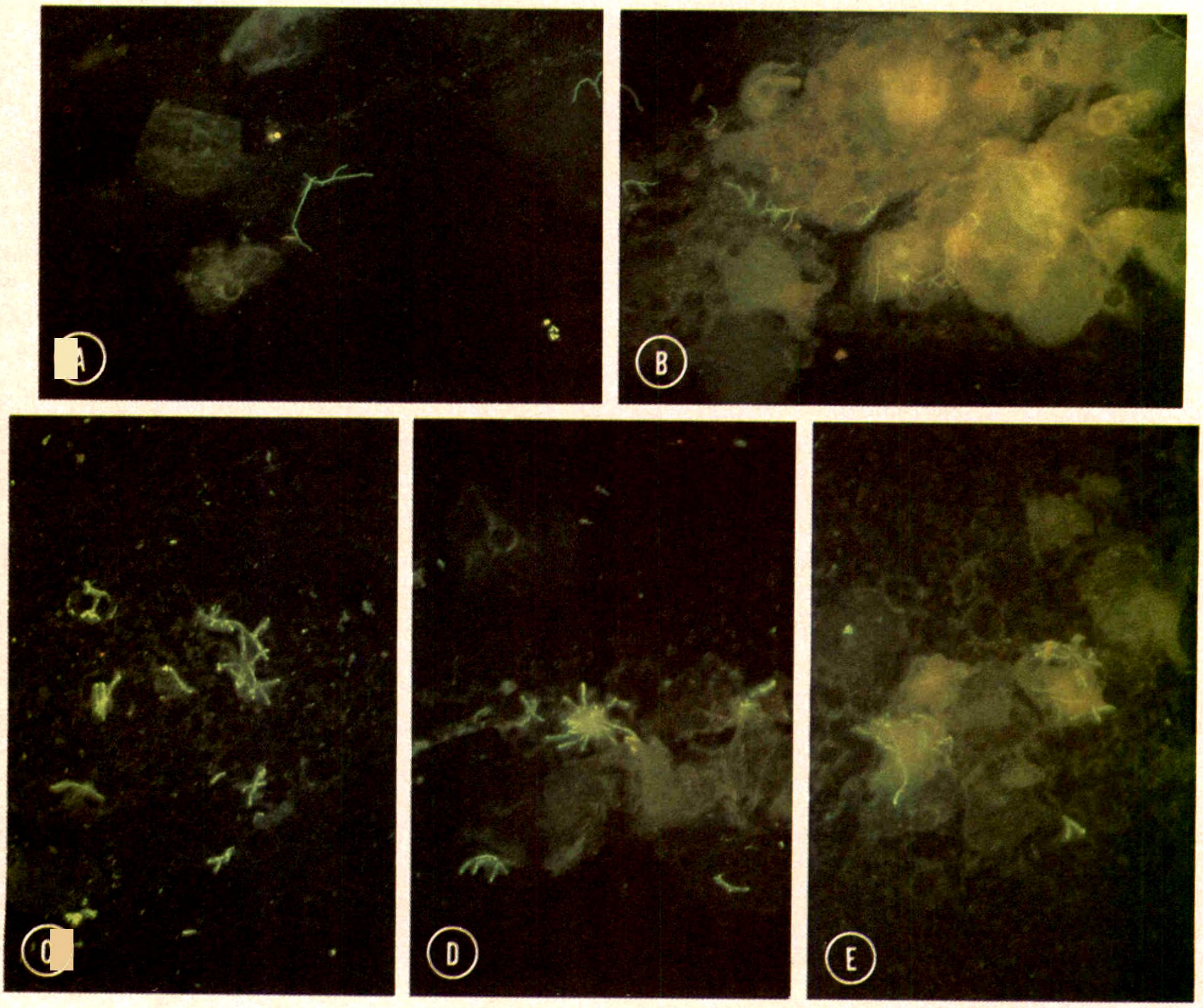

Fig. 2. Fluorescent antibody stains of cervicovaginal smears from an asymptomatic woman with an intrauterine contraceptive device. *A* and *B, A. propionica; C, D,* and *E, A. israelii.* (×400; enlarged ×3.)

spiderlike microcolonies and filaments observed in Fig. 2 are similar if not identical to the actinomycetic elements seen in the pus of chronic invasive actinomycosis. Two points are to be made. First, although the Papanicolaou stain may delineate actinomycotic granules, it will not differentiate between actinomycetes and bacterial masses, and it will fail to reveal numerous microcolonies or single cells, such as those seen in Fig. 2. Second, in our opinion, based on the mycelial form and distribution of the actinomycetic elements, the disseminated populations of *A. israelii* and *A. propionica* seen in Fig. 2 define a patient who has a much greater risk of infection and subsequent invasive disease than one with the mycelial granule seen in Fig. 1.

On the colonized but noninvaded surface membranes of the host, the actinomycetes develop long, branched, interwoven filaments to form a dense mycelial structure commonly observed in tonsillar crypts; these are not unlike the mycelial masses depicted in Fig. 1. In the lacrimal canal, these mycelial masses may become sufficiently large to erode the surface membrane, but invasive disease has never been reported in such cases of surface colonization.[6, 7] This mycelial mass is quite different from the true hard actinomycotic sulfur granule which has radiating clubs surrounding a very dense mycelial center, and which most probably results from an immunologic reaction.[8] We strongly subscribe to the statement of Chandler et al.[9] that, "Actinomycosis should be suspected whenever a compact granule within an abscess contains gram-positive, non–acid-fast branched filaments and is surrounded by eosinophilic clubs." Thus, staining and subsequent observation of granules must clearly distinguish between the actinomycetic granule shown in Fig. 1, the true sulfur granule as found by Valicenti et al.[10] in two patients who were using an intrauterine contraceptive device, and the more recently described pseudosulfur granules associated with intrauterine contraceptive devices as described by O'Brien et al.[11]

Recently, Persson et al.[12] detected *A. israelii* in 4% of the smears from 68 women who used an intrauterine contraceptive device and in 3% of the cervical smears from 68 women who did not use an intrauterine contraceptive device, whereas Jones et al.[13] found no *Actinomyces* in 100 women, 94 of whom did not use an intrauterine contraceptive device. In both studies, a direct fluorescent antibody stain was used. Our findings and those of Persson et al.[12] support the conclusion that *A. israelii* is a commensal of the female genital tract, whereas the findings of Jones et al.[13] do not. In our development of the procedure for fluorescent staining in which we digested the tissue with pepsin and counterstained with rhodamine, we initially dealt with tissue which gave a positive culture of *A. israelii* and a positive methenamine-silver stain for actinomycetes.[14] However, we were unable to demonstrate the ramifying actinomycotic filaments by simple direct fluorescent antibody staining because of the nonspecific staining of tissue membranes; but we obtained an excellent demonstration of this mycelium after pepsin digestion. When we attempted to stain cervicovaginal smears, we were again confronted with the same difficulty when we used the direct fluorescent stain for those smears which had significant amounts of pus cells, debris, and protein material. Indeed, as we reported,[1] we found no *Actinomyces* in our first 25 patients. In our second series, in which the slides were treated with pepsin, the numbers of positive observations were limited to a few cells or cell clusters among 50 women who had used or had not used an intrauterine contraceptive device. However, in the examination of the third group of patients, several cervicovaginal smears of asymptomatic patients had high populations of *A. israelii* and *A. propionica*. These populations of one patient are shown in Fig. 2. In our minds, positive observation of actinomycetes was always associated with smears that contained pus and tissue cells, and our attention was inevitably directed to such slides. Jones et al.[13] pointed out that they did not use pretreatment with pepsin or rhodamine because examination of the Papanicolaou-stained smears or those stained with fluorescein-labeled antibody did not disclose the presence of significant amounts of cellular white cells or debris and red blood cells. We fully agree that, in such slides, *Actinomyces* may not have been present, and also agree that they may have been so few in number as to go unobserved.

Although the specific fluorescent antibody stain for cervicovaginal actinomycetes is a much more sensitive stain than the Papanicolaou stain, application of the fluorescent stain remains greatly limited by the absence of commercially available reagents. Hopefully, such reagents will become available in the near future. However, without the fluorescent antibody stain, there is a much greater chance to completely miss *Actinomyces*-positive populations of the type demonstrated in Fig. 2.

We are indebted to Linda Dix-Zuckerman, Department of Cytology, Biomedical Reference Laboratories, Inc., Burlington, NC, for the photographs in Fig. 1.

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Renal vein thrombosis following puerperal ovarian vein thrombophlebitis

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A case of renal vein thrombosis following puerperal ovarian vein thrombophlebitis is reported. We review the syndrome of puerperal ovarian vein thrombophlebitis and emphasize the potential for renal vein and vena caval involvement. The utility of computed tomographic scanning for diagnostic confirmation of this postpartum complication is described. (AM J OBSTET GYNECOL 1985;152:290-1.)

Key words: Ovarian vein thrombophlebitis, computed tomographic scan

Renal vein thrombosis is a vascular disease of the kidney which occurs most often in patients with nephrotic syndrome or in infants with dehydration. We report an unusual case of renal vein thrombosis in a woman with puerperal ovarian vein thrombophlebitis and illustrate the utility of computed tomography in establishing the diagnosis.

Case report

A 20-year-old black primiparous woman underwent an uncomplicated cesarean section for a 35-week intrauterine twin gestation. On the evening of operation, the fever spiked to 101.4° F. She was started on a regimen of intravenous ampicillin. Cultures of blood and urine specimens obtained prior to institution of therapy were negative for growth. The patient remained febrile and gentamicin and clindamycin were added to the ampicillin regimen for presumed endometritis. Repetitive, diurnal fever spikes occurred but repeat blood and voided urine cultures were negative. On postoperative day 8 the patient complained of left lower-quadrant tenderness and painful urination. An ultrasound examination of the pelvis failed to demonstrate an abscess. Urologic consultation was requested on postoperative day 10 when the patient noted the onset of severe left flank pain. On physical examination the patient appeared mildly ill and complained of left-sided pain. She had left costovertebral angle tenderness to fist percussion but no palpable mass. Pelvic examination disclosed no adnexal mass. Urinalysis was normal and there was no proteinuria. A complete blood count obtained on the day of urologic consultation demonstrated a leukocytosis with a marked left shift (white blood cell count: 15,200/mm^3; 74 segmented granulocytes, 11 bands) and a normal platelet count. An excretory urogram demonstrated poor visualization of

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the collecting structures on the left side, particularly at the lower pole, suggesting an inflammatory process and possibly an abscess in this area. A computed tomographic scan was suggested for confirmation. With contrast augmentation there was demonstrated within the lumen of the inferior vena cava a low attenuation density, corresponding to thrombus, that extended from the intrahepatic portion of the inferior vena cava to the level of the left renal vein. There was also noted a similar low-attenuation density within the left renal vein (Fig. 1). An inferior venacavagram demonstrated a vena caval thrombus from the level of the left renal vein to just below the right atrium. In our attempts to determine the origin of these findings we re-reviewed the computed tomographic scan and were surprised to find a low-attenuation density corresponding to thrombus within the left ovarian vein, which could be traced caudad to the pelvis.

The patient was treated with systemic anticoagulation and antibiotics and was discharged 4 weeks later on a regimen of an oral anticoagulant. A follow-up renal nuclear scintigram demonstrated excellent function in the involved kidney.

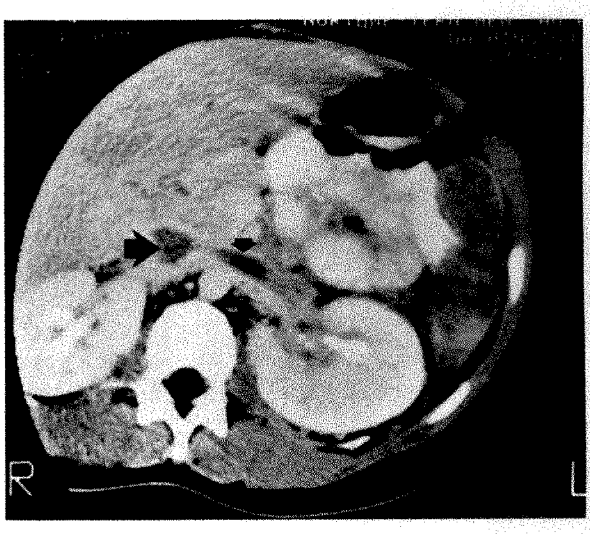

Fig. 1. Computed tomographic scan demonstrating a low-attenuation density (corresponding to thrombus) within the lumen of the inferior vena cava *(large arrow)* and a similar density in the lumen of the left renal vein *(small arrow)*.

Comment

The syndrome of puerperal ovarian vein thrombophlebitis was thought to be a rare postpartum complication until Brown and Munsick[1] reviewed 36 cases and found that the incidence of puerperal ovarian vein thrombophlebitis was 1 in 569 deliveries. They concluded that puerperal ovarian vein thrombophlebitis usually presents as a syndrome consisting of lower abdominal or flank pain, fever, and a tender abdominal mass, the thrombosed ovarian vein. In addition, they reported that the thrombus usually reaches to the vena cava on the right or to the renal vein on the left and may extend into either or both of these major veins. Recommended treatment consists of systemic anticoagulation with heparin and appropriate parenteral antibiotics. Operative intervention (ovarian or vena caval ligation) is justified only when embolism occurs despite proper therapy.[1]

In the past, the diagnosis of puerperal ovarian vein thrombophlebitis has been difficult to confirm with noninvasive imaging studies. Even with renal vein involvement, as in this case, definitive diagnosis is seldom possible. The findings of renal vein thrombosis on an excretory urogram are variable, depending on the rapidity and completeness of the renal vein block; however, the ability of computer-assisted tomographic scanning to reveal thrombosis of the inferior vena cava and its major tributaries provides an excellent noninvasive means of documenting renal vein thrombosis. Abnormal findings include direct demonstration of low-attenuation thrombus in the renal vein, renal vein enlargement, presence of perirenal collaterals, and unilaterally prolonged corticomedullary junction time.[2] Intravenous contrast enhancement rules out venous blood flow within the low-attenuation density. More importantly, as seen in this patient, computed tomographic scanning is also capable of revealing clot within an ovarian vein and should aid in the future diagnosis of puerperal ovarian vein thrombophlebitis. Clinicians should be aware of this syndrome with its potential renal vein and vena caval involvement, the usefulness of computed tomographic scanning in demonstrating ovarian and renal venous thrombosis, and the responsiveness of this clinical syndrome to systemic anticoagulation and broad spectrum antibiotics.

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Interval tubal sterilization in obese women—An assessment of risks

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Obesity is considered to be a complicating factor in most surgical procedures, but very few studies have investigated whether this is true for tubal sterilization. We used a large international data set to investigate the effect of obesity on tubal sterilization. Each of the 159 women delineated as obese (>50% above the mean ideal weight) was matched with a woman of normal weight on important provider variables such as center, operator, and type of surgical procedure. Incidences of anesthesic, surgical, and early postsurgical complications were comparably low and of a mild nature for both the obese and the nonobese groups. Incidence of surgical difficulties was higher, and as a result, the technical failure rate was also higher and the surgical time longer for obese women than for nonobese women. However, none of these surgical difficulties or technical failures led to serious consequences. The difference in surgical times was small and is probably of little practical significance. It appears that the surgical difficulties of tubal sterilization in moderately obese women can be easily overcome. (AM J OBSTET GYNECOL 1985;152:292-7.)

Key words: Tubal sterilization, obesity, laparoscopy, minilaparotomy, culdoscopy

At one United States center, 3.1% of the 1604 women undergoing laparoscopy for sterilization or diagnosis weighed more than 200 pounds.[1] A Mexican center reported that a high proportion (58.5%) of the 800 women sterilized by minilaparotomy were obese, defined as ≥5 kg above the ideal weight according to the Metropolitan Insurance Company standard.[2] While these two examples may be extreme, the actual number of obese women requesting sterilization certainly is unlikely to be small, considering that, in 1980, more than 50 million women worldwide were estimated to be controlling their fertility by sterilization.[3]

Obesity is a factor complicating most major surgical procedures. Whether this is also the case for tubal sterilization, an elective, generally minor, but delicate procedure, has rarely been the exclusive focus of a study. This report, based on a large international data set of tubal sterilization, is an attempt to answer the following questions:

1. Are obese women in general, when undergoing an interval tubal sterilization procedure, subject to an increased risk of mortality, morbidity, and/or operative problems as compared to nonobese women?
2. If so, what are the specific types and magnitudes of the risks, and how do these risks relate to the type of sterilization procedure?

Material and methods

A total of 31,320 women undergoing interval tubal sterilization (that is, >42 days after the last pregnancy ended) for contraception were consecutively admitted to the international study coordinated by Family Health International between 1972 and 1979. Standardized forms and definitions of terms were used to record the women's sociodemographic characteristics, reproductive and contraceptive histories, weight (kilograms) and height (centimeters), medical history and preexisting conditions, type of sterilization procedure performed, and problems and complications encountered during and after the procedure, before discharge, and at early follow-up visits, usually 7 to 21 days after discharge.

We excluded those patients who were nulliparous, had no information on weight and height, or had a concurrent surgical procedure at the time of sterilization. (Those who had a concurrent surgical procedure that was a consequence of a complication of the sterilization procedure were not excluded.) Thus our study population consisted of 24,850 sterilization patients from 17 centers located in five more developed countries and 76 centers in 23 less developed countries.*

By the classification of Hanna et al.,[5] obesity was defined as a body weight more than 50% greater than the

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*More developed and less developed countries were divided according to the list of reference 4. More developed countries include Belgium, England, Netherlands, Singapore, and United States. Less developed countries include Bangladesh, Brazil, Chile, Colombia, Costa Rica, Egypt, El Salvador, India, Iran, Jamaica, South Korea, Lebanon, Nepal, Malaysia, Mexico, Nigeria, Pakistan, The Philippines, Sri Lanka, The Sudan, Taiwan, Thailand, and Turkey.

Table I. Type of anesthesia and tubal occlusion technique by surgical approach for the 159 obese/nonobese pairs of women undergoing tubal sterilization

	Surgical approaches		
	*Minilaparotomy**	*Laparoscopy*	*Vaginal†*
Type of anesthesia			
General	20	50	7
Spinal	2	—	23
Local/analgesia	5	35	17
Tubal occlusion technique			
Ligation	18	11‡	22
Electrocoagulation	—	35	—
Tubal ring	8	27§	—
Clip	1	12	25

*Six laparotomy cases are included in minilaparotomy category.

†Forty cases by culdoscopy and seven cases by colpotomy.

‡All were operated on by the El Kady method. In this method a laparoscope is used to visualize the tubes, which are then elevated and ligated through the 2 cm wound incision.

§Includes five cases by needlescope and one case by open laparoscopy.

mean ideal weight for a medium-frame woman according to the Metropolitan Insurance Co. standard.[6] A total of 165 women from the data set were delineated as obese. Each of these obese women was matched with a woman within the normal ranges of relative weight of the Metropolitan Insurance Co. standard for a medium-frame woman (hereafter the nonobese women) who had undergone the same type of surgical approach and tubal occlusion technique under the same type of anesthesia (local, spinal, or general) at the same center by the same operator around the same time. A total of 159 pairs were successfully matched.*

Table I shows the tubal occlusion techniques and type of anesthesia used by type of surgical approach for these 159 matched pairs.

The obese and nonobese women were compared for patient characteristics and preexisting conditions and then for the following outcome variables: anesthetic problems, surgical difficulties, technical failures, surgical complications, time spent in the procedure, and complications and complaints before discharge and at first follow-up.

Paired t tests and matched χ^2 tests were used for comparing quantitative and categorical data, respectively. Two-tailed tests were used for comparisons of patient characteristics or preexisting conditions and one-tailed tests for comparisons of the outcome variables, based on the assumption that obesity is usually an undesirable condition for any surgical procedure. A difference with $p < 0.05$ or an odds ratio with the 95% confidence limits not including unity was considered statistically significant.

Table II. Surgical difficulties encountered in the 159 obese/nonobese pairs of women undergoing tubal sterilization

	Obese women	*Nonobese women*
Reported as obesity related	22	—
Probably obesity related for obese women		
Difficulties in visualizing and/or occluding tubes	3	1
Difficulties in application of the instruments	2	—
Difficulties in entering the peritoneal cavity	1	1
Less likely obesity related for obese women		
Inadequate anesthesia	2	2
Pelvic adhesion	1	4
Gas leakage	1	1
Retroverted uterus	1	—
Difficulties in manipulation of uterus	—	1
Total	33	10

Results

Patient characteristics and preexisting conditions. The obese women were, on the average, 1 year older and had one more live birth than their nonobese counterparts. Also, proportionately, more obese women (19.5%) than nonobese (10.7%) had used an intrauterine contraceptive device for contraception during the last month prior to sterilization. These differences were statistically significant. None of the following characteristics or conditions was significantly different be-

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*Fifteen obese women were matched with slightly obese women (10% to 20% over ideal weight) and two with mildly obese women (20% to 30% over ideal weight).

Table III. Technical failures in the 159 obese/nonobese pairs of women undergoing tubal sterilization

Planned procedure	*Procedure changes*	*Reason for failure*	*Weight (kg)*
Obese women			
Obesity related			
Laparoscopic, tubal ring	Laparoscopic cautery	Trocar could not reach abdominal cavity	90
Laparoscopic, tubal ring	Laparoscopic cautery	Instrument defect due to obesity	92
Culdoscopic, clip	Procedures discontinued	Poor visualization of tubes	90
Less likely obesity related			
Colpotomy, Pomeroy	Salpingectomy of left tube	Difficulty in delivering tubes	≥98
Laparoscopic, tubal ring	Laparoscopic cautery	Applicator problem	95
Culdoscopic, clip	Procedure discontinued	Uterine fibroid	96
Laparoscopic, cautery	Laparotomy, Pomeroy	Inadequate pneumoperitoneum	80
Minilaparotomy, tubal ring	Laparotomy, Pomeroy	Tubes locked in ring applicator	80
Nonobese women			
Colpotomy, Pomeroy	Salpingectomy of right tube	Tube injury	65

tween the two groups: number of years of education received, urban/rural residence, number of previous abortions (spontaneous or induced), number of stillbirths, diabetes, previous abdominal surgery, or pelvic infections.

Complications and problems during or immediately after the procedure, and surgical time

Anesthetic complications. Although two thirds of the 159 pairs received general or spinal anesthetics, only mild anesthesia-related complications were reported from four obese women (three vomiting and one short-term apnea) and three nonobese women (all vomiting).

Surgical difficulties. Surgical difficulties refer to technical difficulties encountered in performing the sterilization procedure. The operators reported surgical difficulties in 33 obese women (20.8%) and in only 10 nonobese women (6.3%). The matched odds ratio is 4.3 (one-tailed 95% confidence limit: 2.07 to 9.83).

As shown in Table II, two thirds of the difficulties (22 of 33) in the obese group were reported as directly related to obesity, but the types of difficulties were not specified. Another six difficulties in the obese women were probably related to obesity as judged by us. It is difficult to assess the contribution of obesity in the remaining five reported difficulties. In contrast, for the 10 nonobese women with surgical difficulties, four were due to pelvic adhesion and two to anesthesia problems.

Technical failures. Technical failures (or failed attempts) are defined as failures to complete the planned sterilization procedures because of surgical difficulties, complications, or instrument defects (for instance, breakdown of the laparoscope) so that either the procedures were left uncompleted or the operator switched to other approaches or techniques.

Technical failures occurred in eight (5.0%) of the total 159 obese women, but only three of the eight failures were reported to be related to obesity. There was one technical failure (0.6%) in the nonobese group. The difference is statistically significant ($p = 0.012$ by matched χ^2 test.)* The types of failures and relevant information by planned procedure are shown in Table III.

Surgical complications. No serious events such as death, shock, or bowel/bladder injury occurred in either the obese or the nonobese group. One patient from each group had excessive bleeding during the procedure, but neither required transfusion.

Seven obese women suffered tubal/mesosalpingeal injuries during the procedure (three with bleeding and four without). Similarly, six nonobese women suffered surgical complications but with more varieties: three with tubal/mesosalpingeal injuries (one with bleeding), one with uterine perforation, one with peritoneal injury with bleeding, and one with the occlusive procedure applied to the wrong structure.

Surgical time. Technical failures were excluded from comparisons on time spent in the sterilization procedures (from incision to suture). The procedures took, on the average, 17.5 minutes (SD 12.4) for the obese and 14.2 minutes (SD 8.3) for the nonobese to complete. When patients with surgical difficulties were excluded, the mean surgical time was slightly reduced to 16.8 minutes for the obese and there was no change for the nonobese. Differences in surgical time between the two groups of women, regardless of whether surgical difficulties were included or excluded, were statistically significant.

Complications and complaints before discharge and at early follow-up. Fifteen obese women and 15 nonobese women suffered minor complications (mostly pelvic pain) before discharge. Ninety-nine of the obese women (62.3%) and 105 of the nonobese (66.0%) were discharged on the day of the procedure.

Among the obese women 150 (94.3%) and among

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*The matched odds ratio is undefined because of the small number of technical failures; the lower limit of this risk for a one-sided confidence interval is 1.9.

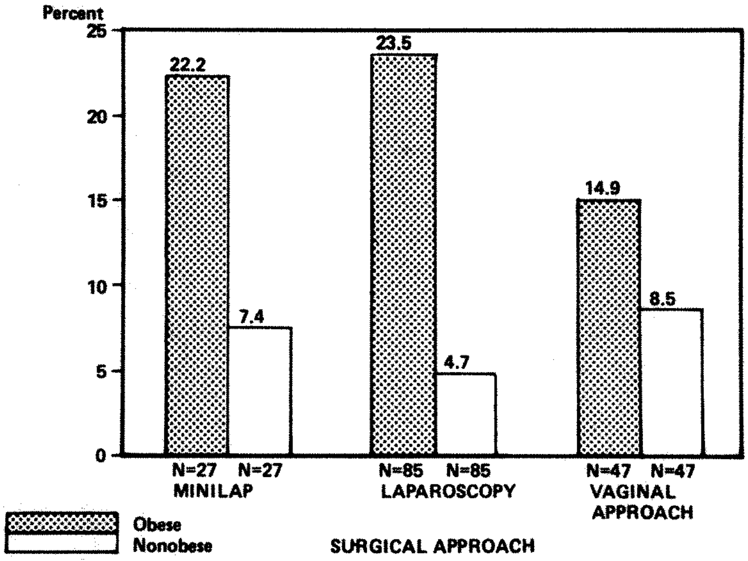

Fig. 1. Percent with surgical difficulties for obese and nonobese women by type of surgical approach. *Minilap,* Minilapartomy.

the nonobese 152 (95.6%) came back to the same clinic for a checkup 7 to 21 days after discharge. Eleven obese and 11 nonobese women had fever requiring antibiotics or complained of mild prolonged bleeding during this period. Two readmissions, however, were necessary: One obese case due to an incision wound infection and one nonobese case due to pelvic peritonitis.

Comment

An array of complications and problems has been related to obesity in tubal sterilization studies: anesthesia problems,[7-9] difficulties in inducing pneumoperitoneum,[8, 9] difficulties in maneuvering the laparoscope or the laparoscopic sheath being too short to reach the peritoneal cavity,[10] injury or perforation of major vessels[2] and organs,[11] and increase of technical difficulties[12] as well as length of operating time.[13] However, either these assertions were based on small numbers, not supported by any data, or included no adequate comparison group(s).

The international data set used here was obtained from 38 centers located in 16 countries with different degrees of sophistication and adequacies of facilities as well as varying degrees of staff experience and skills in tubal sterilization. Also, this data set covered the most commonly used types of surgical and tubal occlusion techniques. Thus the findings will give a more representative picture, will have a wide applicability, and will not likely be biased by a special pattern of one center, one operator, or one specific technique.

One hundred sixty-five of the 24,850 women in our original study population were screened as obese, representing a prevalence rate of 6.6/1000 women requesting tubal sterilization. The median weight for the obese group was 91 kg, with 50% of the weights falling between 87 and 96 kg. The median was 54 kg for the nonobese group, and 50% of the weights for this group fell between 50 and 60 kg. There were no overlaps in either the relative or the actual weights between the two groups.

The incidences of anesthesia complications, surgical complications, and early complications were similarly low and rarely of a serious nature for obese or nonobese women. Lengths of hospitalizations were also short, with two thirds in each group discharged on the day of the procedure.

Because of the matching of operators and operation dates, the lack of differences for these complications between the obese and nonobese in this study is not likely to be biased by the possible tendency for obese women to be operated on by the more experienced staff in a center. These findings agree with the results of the previously mentioned United States study on laparoscopy[1] and the Mexico study on minilaparotomy[2] in which obese women were exclusively examined.

The three outcome variables found to be statistically different between the obese and nonobese women are surgical difficulties, technical failures, and surgical time. When adjusted simultaneously by the method of Breslow et al.[14] for age, number of live births, and previous use of intrauterine contraceptive devices, the odds ratios and magnitude of differences for the three outcome variables did not substantially change, so that the differences are not due to confounding.

The incidence of surgical difficulties encountered in these 159 obese women (20.8%) was the highest in the

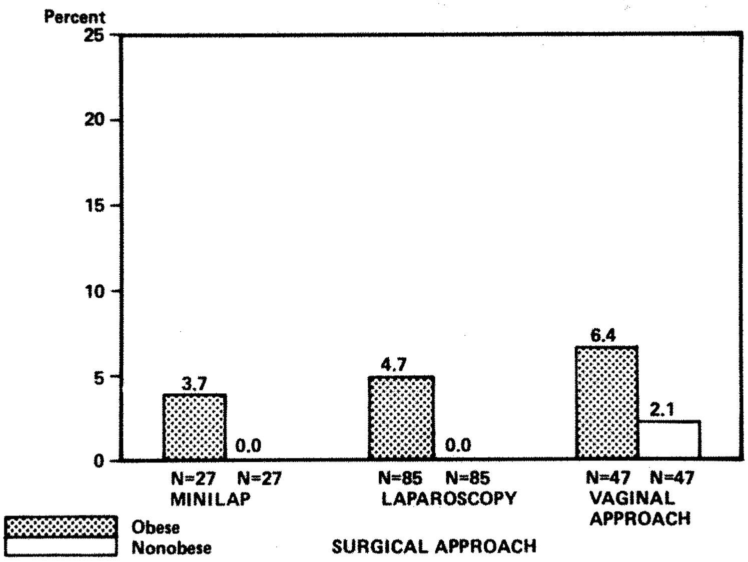

Fig. 2. Percent with technical failures for obese and nonobese women by type of surgical approach.

literature on tubal sterilization,[12, 15] even higher than the 18.0% rate reported for women who had had previous abdominal operations and had undergone laparoscopic sterilization.[16] The 33 obese women with surgical difficulties were reported from 17 of the 38 study centers and from the developed as well as the developing countries, negating the possibility of a center-clustering effect.

Rates of surgical difficulties were consistently higher for the obese than the nonobese for laparoscopy, minilaparotomy, and the vaginal approach, but the most marked difference was for the laparoscopic approach with an odds ratio of 6.23 (Fig. 1).

For five of the eight technical failures occuring in obese women, the occlusion techniques were easily switched to other tubal occlusion techniques. One laparoscopy, however, required laparotomy to complete the procedure and two culdoscopic sterilizations were left uncompleted (one was obesity related). Incidence of technical failures for the obese and nonobese groups by surgical approach is shown in Fig. 2.

The surgical time was consistently longer in the obese than the nonobese women for the three types of surgical approaches. The difference was largest (7 minutes) in minilaparotomy sterilization. For the laparoscopic sterilization, the difference was only 1.5 minutes and is probably of little practical significance for either the clinic or the patient. In total, the difference remained statistically significant even after patients with surgical difficulties were excluded, suggesting that obesity does add a few minutes to the length of the procedures (such as lengthening the time for incision of the abdominal wall and peritoneum as well as for locating the tubes), even in patients for whom no surgical difficulty was reported.

When the three outcome variables are considered together, it appears that technical failures as well as longer surgical time were, either totally or partially, a result of surgical difficulties. These surgical difficulties, however, rarely resulted in serious consequences.

It should be mentioned at this juncture that only 36 women in our obese group weighed ≥98 kg; thus our findings here may not apply to extremely obese women for whom more studies are needed. Also, the number of obese women sterilized by minilaparotomy or the vaginal approach was too small to study the adverse effects of these surgical procedures.

Finally, while the experience and skill of the operators are undoubtedly important factors determining the outcome of a surgical procedure, especially in patients with preexisting conditions, this effect was not addressed here because of the matched design in this analysis dealing with a multicenter data set. However, since our study involved 38 centers in developed and developing countries and close to 100 operators with differing degrees of experience in tubal sterilization, it is probably not too difficult for the operators to gain the experience necessary to deal with an adverse condition such as moderate obesity in interval tubal sterilization.

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Intrapartum external cephalic version

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Intrapartum external cephalic version at term was employed in 15 patients with intact membranes and breech presentations; successful version occurred in 11 patients. There were no untoward maternal or fetal outcomes. (AM J OBSTET GYNECOL 1985;152:297-8.)

Key words: Intrapartum external cephalic version, breech presentation, fetus

Antepartum external cephalic version with tocolysis has been reported to be an efficacious maneuver to reduce the incidence of breech presentation at term.[1-3] Despite our attempts to screen all pregnant women for breech presentations and perform antepartum external cephalic version,[1] we continued to encounter laboring women with breech presentations in whom antepartum external cephalic version had not been attempted. This report details our experience with intrapartum external cephalic version with tocolysis.

Patients and methods

Twenty-two pregnant women at term were studied from June 1980 through November, 1982. The patients presented in active labor with breech presentations. Although an antepartum external cephalic version with tocolysis protocol was in effect,[1] these patients either were not diagnosed as having breech presentations, declined an antepartum external cephalic version, or had not received prenatal care. Early in the study intrapartum external cephalic version was attempted on patients whose membranes had spontaneously ruptured; however, the procedure was noted to be uniformly unsuccessful in these patients. Therefore only those women with intact membranes in whom intrapartum external cephalic version was attempted are included in this report (n = 15). These patients were not considered to be candidates for breech vaginal delivery by their attending physicians. If the fetal heart tracing was unremarkable, ultrasound examination normal, and one of the authors was available to perform the procedure, the patient was offered an intrapartum external cephalic version under tocolysis after informed consent was obtained. Ritodrine hydrochloride was generally used for tocolysis; in addition, three patients had versions performed while they were under epidural anesthesia. The procedure was performed in an operating room with the capability for immediate cesarean delivery. During the attempted version, ultrasound was used to assess the fetal heart tones and to help delineate the intrauterine anatomy. Patients with multiple gestation, vaginal bleeding, or placenta previa

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Table I. Intrapartum external cephalic version in patients with intact membranes

Patient	*Gestational weeks of age*	*Parity*	*Cervical dilatation*	*Version outcome*	*Route of delivery*	*Apgar scores*	*Birth weight (gm)*
1	39	0	1	S	MFD	6, 9	3640
2	40	1	8	S	SVD	8, 9	3150
3	41	4	5	S	SVD	8, 9	3980
4	38	3	6	S	ELF	7, 9	2980
5	40	0	2	F	CS	2, 10	4160
6	40	1	3	S	SVD	9, 9	3475
7	41	0	3	F	CS	6, 9	3150
8	39	0	4	F	CS	6, 8	2910
9	40	0	2	F	CS	8, 9	3033
10	40	1	8	S	SVD	8, 9	3450
11	39	0	4	S	CS	6, 9	3160
12	37	1	2	S	SVD	7, 8	2870
13	40	2	4	S	SVD	9, 9	3351
14	38	1	1	S	SVD	7, 9	3106
15	40	2	3	S	SVD	8, 9	3300

S = Successful; F = failed; MFD = midforceps delivery; SVD = spontaneous vaginal delivery; ELF = elective low-forceps delivery; CS = cesarean section.

were excluded. Patients in whom version was successful were returned to the labor and delivery suite for further management of labor after continuous monitoring of the fetal heart rate for 30 minutes. Maternal and fetal outcomes were noted.

Results

Patient data and outcome are outlined in Table I. As can be noted, version was successful in 11 of 15 patients (73%). Vaginal delivery occurred in 10 of the 11 patients; the remaining patient was delivered by a primary low transverse cesarean section because of secondary arrest of cervical dilatation. Bradycardia occurred during the version procedure in four instances (27%). In no case was the bradycardia longer than 2 minutes in duration and in all instances the bradycardia responded to temporary suspension or completion of the procedure. There was no evidence of abruptio placentae and no maternal complications were noted. All infants were vigorous at birth and in no infant did careful newborn evaluation reveal any adverse effects from the attempted version.

Comment

From the results of our experience, it appears that intrapartum external cephalic version may be a reasonable alternative for the patient with a breech presentation in labor in whom an antepartum external cephalic version has not been attempted. In our patients the procedure was well tolerated and no maternal or fetal/neonatal complications occurred. The overall success was encouraging. The procedure was performed in the operating room where immediate delivery was possible in case of an untoward event such as spontaneous rupture of the membranes with associated prolapsed cord. When used within these guidelines the procedure does not appear to threaten maternal or fetal well-being.

Intrapartum external cephalic version is not recommended as a replacement for antepartum external cephalic version but instead is described as a procedure to be considered for the laboring patient in whom an antepartum procedure has not been attempted for various reasons. Although the numbers are small, intrapartum external cephalic version is only rarely, if ever, successful after rupture of the fetal membranes has occurred. In our series, successful performance of intrapartum external cephalic version obviated the need for cesarean sections in 10 women who were not considered to be candidates for vaginal breech deliveries. A large scale prospective randomized trial of intrapartum external cephalic version under tocolysis may be indicated to further address the issues of safety and efficacy and to determine the ultimate place in our obstetric armamentarium for this procedure.

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Doubling times of human chorionic gonadotropin increase in early viable intrauterine pregnancies

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Although the doubling time of serum human chorionic gonadotropin has been assumed to be constant in early viable intrauterine pregnancy (prior to 6 to 7 weeks after menses), the range has varied between 1.4 and 3.5 days in the literature. To evaluate this variability of the doubling time, the mean doubling times at different ranges of human chorionic gonadotropin concentrations were determined in 49 normal pregnancies, and the doubling times at different intervals of gestation from both the day of the basal body temperature shift and the last menstrual period. The data obtained from the three different methods indicate that the doubling time of human chorionic gonadotropin is not constant but rather increases with increasing human chorionic gonadotropin concentration or gestational age. In addition, statistical analysis of the semilogarithmic plots of serum human chorionic gonadotropin concentrations indicated that the exponential rate of increase of serum human chorionic gonadotropin significantly decreases with gestational age. Since serum human chorionic gonadotropin doubling times increase and the exponential rate decreases with gestational age, estimates of normal values should be established for small sampling ranges and/or short intervals of gestation. (Am J Obstet Gynecol 1985;152:299-302.)

Key words: Chorionic gonadotropin, human; pregnancy, early monitoring; chorionic gonadotropin, doubling times; gonadotropin

Serial determinations of serum concentrations of the β-subunit of human chorionic gonadotropin (β-hCG) have been shown to be useful in evaluating early pregnancies.[1-6] Although the doubling time of β-hCG concentrations has been assumed to be constant in early viable intrauterine pregnancies, the range has varied between 1.4 and 3.5 days.[3-10] Review of the literature suggests that the value may depend on how early in the gestation the doubling time is determined (Table I). For example, a doubling time of 1.4 days was determined in a study examining β-hCG concentrations in the late luteal phase and first week after the anticipated menses,[9] while values between 2.0 and 3.5 days were obtained from the fourth to eighth week after the previous menses.[3, 4, 6, 10] The higher estimates of the doubling time tended to have more data points in the sixth to eighth week.[6, 10] To evaluate the variability of the doubling time and to define more precisely the normal values, we examined serial β-hCG determinations in 49 normal pregnancies prior to the eighth postmenstrual week.

Method and materials

Serial β-hCG determinations were performed on serum samples obtained from 49 infertile women who conceived while they were patients at the Center for Fertility and Reproductive Research. All pregnancies progressed to at least 32 weeks' gestation and resulted in the delivery of viable infants. Menstrual calendars recording the onset of the last menses and basal body temperature charts were available for 42 and 35 women, respectively. The first serum samples were obtained to confirm pregnancy and subsequent samples were drawn usually at 2- to 4-day intervals. The date and time of day for each blood sample were recorded.

The double-antibody assay for β-hCG has been previously described.[11] The National Institutes of Health β-hCG antiserum and the CR-119 hCG reference preparation were used. One nanogram of this preparation corresponds to approximately 5 to 6 mIU of the second international reference preparation. The doubling time was defined as the number of days required for the serum β-hCG concentration to double and was calculated from two concentrations obtained from the same woman, 2 to 4 days apart, according to the following formula:

$$\text{Doubling time} = \frac{(\log 2) \times (\text{time interval in days})}{\log\frac{[\text{hCG}_2]}{[\text{hCG}_1]}}$$

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Table I. Doubling times of serum β-hCG in viable pregnancies determined from linear regression equations

Author	*Sampling period*	*No. of patients*	*Doubling time (days)*
Chartier et al.,[9] 1979	10-22 days after BBT nadir	57	1.4
Marshall et al.,[7] 1968	11-21 days after administration of hCG	7*	1.7
Cartwright and DiPietro,[5] 1984	11-32 days after insemination	27	1.9
Braunstein et al.,[8] 1973	0-20 days after detection of hCG	4	2.0
Kadar et al.,[1] 1982	29-64 days after LMP	26	2.0
Batzer et al.,[3] 1981	12-30 days after BBT shift	189	2.2
Aspillaga et al.,[10] 1983	28-60 days after LMP	20	3.3
Lagrew et al.,[6] 1983	28-60 days after LMP	57	3.5†
Present study	13-20 days after BBT shift	18	1.5
	13-25 days after BBT shift	26	1.9
	13-30 days after BBT shift	30	2.2
	13-39 days after BBT shift	35	2.7
	28-35 days after LMP	17	1.4
	28-42 days after LMP	35	2.2
	28-49 days after LMP	40	2.5
	28-56 days after LMP	42	2.9

BBT = Basal body temperature; LMP = last menstrual period.

*One spontaneous abortion.

†Calculated from the authors' data.

Table II. Doubling times (dt) of serum β-hCG concentrations determined by three methods

			Multiple linear regression			
			BBT		*LMP*	
*Sampling range (ng/ml)**	*DT*	*No. of samples*	*Day*	*DT (n = 35)*	*Day*	*DT (n = 42)*
1. 2-200	1.6	13	13-20	1.5	28-35	1.4
2. 200-1000	2.0	14	20-25	2.4	35-42	2.7
3. 2-1000	1.8	31	13-25	1.9	28-42	2.2
4. 100-(1000-3000)	2.5	9	16-32	2.8	28-49	2.5
5. 1000-5000	3.4	9	25-34	3.5	41-49	3.3

DT = Doubling time; BBT = basal body temperature shift; LMP = time after last menstrual period. 1 versus 1, $p < 0.01$; 1 versus 4 and 5, $p < 0.001$; 2 versus 4, $p < 0.05$; 2 versus 5, $p < 0.01$; 4 versus 5, $p < 0.01$.

*1 ng/ml = 5 to 6 mIU/ml.

where log represents the natural logarithm (base "e") and $[hCG_1]$ and $[hCG_2]$ are the first and second serum hCG determinations, respectively. The differences in the mean doubling times were evaluated by *t* tests (two-tailed).

For comparison, mean doubling times were also computed for women who had basal body temperature data and for those who had last menstrual period data from slope estimates determined from linear least-squares regression, doubling time $= \frac{\log 2}{\text{slope}}$.

To examine whether the exponential rate of increase in hCG concentration significantly decreases with gestational age, a statistical comparison between a linear regression (days of gestation) and a quadratic regression equation (days of gestation squared) was made for the women who had last menstrual period data and for those women who had basal body temperature data. To assure that each observation (hCG determination) was an independent variable, one observation from each woman was randomly selected. Final descriptive linear and quadratic equations were determined for all the available data. Then *t* tests were performed to determine whether there was a significant decline in the exponential rate of increase in hCG concentrations.

Results

The sequential linear regressions of the serum β-hCG concentrations for days after the last menstrual period (Fig. 1) and for days after the basal body temperature shift (Fig. 2) revealed a decreasing exponential rate of increase with gestational age, that is, an increasing doubling time. The doubling times calculated from the slopes of the linear regression equations are shown in Table I and ranged from 1.4 to 1.5 days early in the pregnancy to 2.7 to 2.9 days when determined from all the β-hCG concentrations obtained during the fourth to the eighth postmenstrual week. The

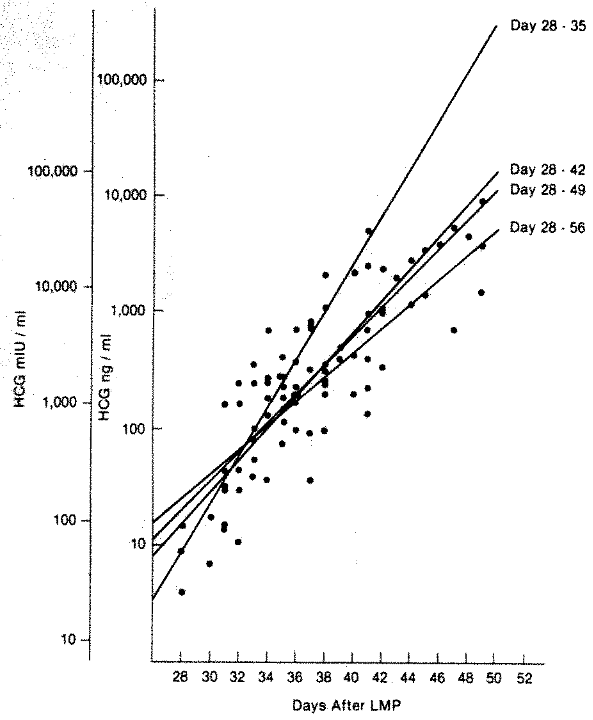

Fig. 1. Sequential linear regression analysis of the serum β-hCG concentrations in normal pregnancies during the first 56 days after the last menstrual period *(LMP)*. Because of spatial considerations, the data points from days 50 to 56 are not shown.

different values of doubling time from the literature are shown in the order of increasing doubling time for comparison.

In Table II are shown the mean doubling times calculated from individual doubling times obtained within the five designated sampling ranges (range 1 to range 5). The sampling ranges of 2 to 200 ng/ml (range 1) and 200 to 1000 ng/ml (range 2) corresponded approximately to days 13 to 20 and 20 to 25 of the basal body temperature shift and days 28 to 35 and 35 to 42, respectively, after onset of last menses. Sampling range 3 included all doubling times in ranges 1 and 2 plus four doubling times that could not be placed in range 1 or 2. Range 4 included initial hCG determinations between 100 and 1000 ng/ml and the second determination in the 1000 to 3000 ng/ml range. Statistical evaluation of the mean doubling times demonstrated significant increases of the values with advancing gestational age, including the early sampling ranges (1 versus 2, $p < 0.01$). For comparison, the corresponding values of doubling time determined from linear regression analysis of data from both basal body temperature and last menstrual period are included. A trend of the doubling times to increase as the pregnancies progresssed, from a low of 1.4 to 1.5 to a high of 3.3 to 3.5, was seen with these methods.

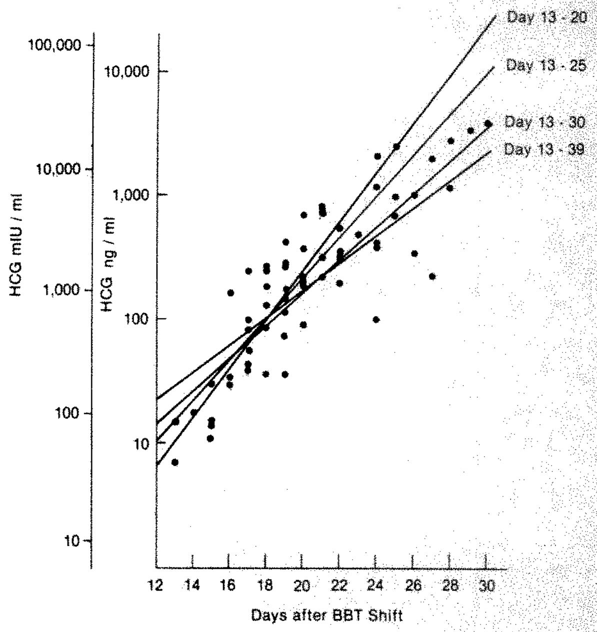

Fig. 2. Sequential linear regression analysis of the serum β-hCG concentrations in normal pregnancies during the first 39 days after the basal body temperature *(BBT)* shift. Because of spatial considerations the data points from day 31 to 39 are not shown.

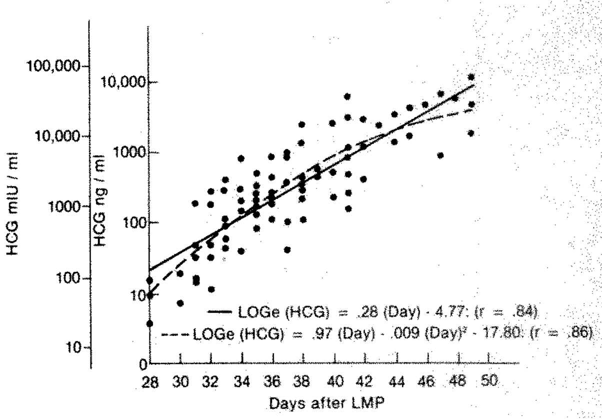

Fig. 3. Comparison of the linear regression analysis with a quadratic regression analysis of the serum β-hCG concentrations in normal pregnancies during the first 49 days after the last menstrual period *(LMP)*.

Furthermore, the exponential rate of increase in hCG concentration significantly decreased with gestational age, as demonstrated by the statistical comparison between the linear and quadratic equations. The quadratic equations based on either the last menstrual period data ($t_{39} = -2.33$, $p < 0.03$) or the basal body temperature data ($t_{32} = -2.91$, $p < 0.01$) described significantly more of the variability of the data than did the linear equations. In addition, the quadratic terms in both equations were negative, indicating that as gestational age increased, the exponential rate of increase

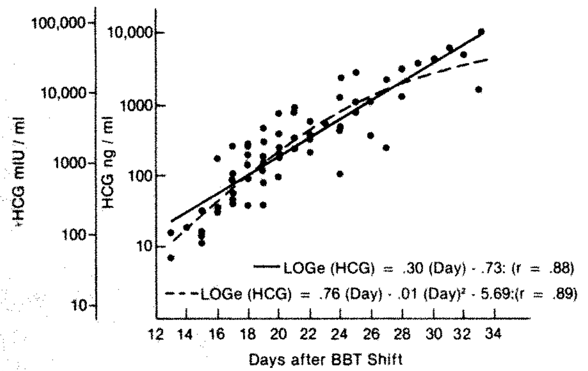

Fig. 4. Comparison of the linear regression analysis with a quadratic regression analysis of the serum β-hCG concentrations in normal pregnancies during the first 33 days after the basal body temperature *(BBT)* shift.

in hCG concentration decreased. The final descriptive equations and their correlation coefficients are given in Figs. 3 and 4. The correlation coefficients for both the linear and quadratic equations were higher when the gestational age could be estimated more precisely, for instance, basal body temperature shift versus time from last menstrual period.

Comment

The normal values of the hCG doubling time in early pregnancy have not been clearly defined in the literature and have ranged from 1.4 to 3.5 days. Although previously described as linear,[1, 5-10] the present study demonstrates that the exponential rate of increase of serum hCG concentrations is not constant during the first 7 postmenstrual weeks of normal pregnancies. The nonlinear relationship is supported by two different methods of examining the data. First, a significant difference in the mean values for the doubling times were observed with advancing gestational age. Second, the statistical evaluation based on both data from time from the last menstrual period and data from the basal body temperature shift revealed that a quadratic equation with a negative quadratic term described the data significantly better than a linear equation, that is, the quadratic equation represents a better mathematical description of the data.

The determination of normal values in a nonlinear relationship is complex. When small sampling ranges or short intervals of time are used as was done in this study, the linear equation derived from the data represents a close approximation of the quadratic curve. Consequently, we are recommending that normal values for the doubling times of hCG concentrations should be established for small sampling ranges and/or short intervals of gestation. For example, doubling times from the first detection of hCG to approximately the thirty-fifth day after the onset of last menses were determined to be 1.4 to 1.6 days and from the thirty-fifth day to the forty-second day to be 2.0 to 2.7 days. With a more precise definition of normal values for the doubling time, the usefulness and sensitivity of serial hCG determinations in the early detection of abnormal pregnancies may be improved.

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Syndrome of camptodactyly, ankyloses, facial anomalies, and pulmonary hypoplasia (Pena-Shokeir syndrome): Obstetric and ultrasound aspects

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Two siblings with Pena-Shokeir syndrome are described. This syndrome consists of polyhydramnios, intrauterine growth retardation, short umbilical cord, perinatal death, facial abnormalities, limb abnormalities including arthrogryposis, and lethal pulmonary hypoplasia. The mode of inheritance is most likely autosomal recessive. Prenatal diagnosis was made in the second pregnancy with ultrasound performed at 26 weeks' gestation. The roles of fetal akinesia and fetal apnea in the production of the various manifestations of the syndrome are detailed, and the possibility of early prenatal diagnosis is considered. (AM J OBSTET GYNECOL 1985;152:303-7.)

Key words: Pulmonary hypoplasia, polyhydramnios, limb deformities, short umbilical cord

In 1974, Pena and Shokeir described a lethal syndrome consisting of facial anomalies, camptodactyly, multiple ankyloses, and pulmonary hypoplasia occurring in two sisters.[1] In the same journal, Punnett et al.[2] described two newborn infants with almost exactly the same clinical condition. Since then, 25 additional examples of this syndrome have appeared in the literature, bringing the total to 29.[3-15] The present article describes two siblings with the syndrome. The literature will be reviewed and important obstetrical and ultrasound considerations will be discussed.

Case reports

Case 1. A 29-year-old white primigravid woman was seen in consultation because of the sudden appearance of polyhydramnios in the thirty-second week of her first pregnancy. Laboratory tests indicated Rh-negative blood type, negative antibody screen, and normal postprandial blood glucose. Examination revealed the presence of polyhydramnios, which was confirmed by ultrasound. Other ultrasonic observations included absent stomach echo and absent fetal respirations. Amniocentesis was performed to check for the possibility of a chromosomal abnormality. The karyotype was 46,XX; amniotic fluid α-fetoprotein was less than 7.5 μg/ml.

Pedigree analysis was negative for congenital anomalies and unexplained stillbirths or neonatal deaths. The couple was of Italian extraction, not knowingly related, and in excellent health. The paternal age was 27.

Spontaneous rupture of the membranes occurred 5 days later, and cesarean section was performed for a premature breech presentation. During the delivery a short umbilical cord was avulsed from its abdominal attachment. The baby's lungs could not be adequately aerated and she died at 17 hours of age.

Autopsy report. The female infant weighed 1540 gm. The cranium had prominent frontal bossing. The nasal bridge was flat; hypertelorism was present. The ears were low-set and malformed. Flexion contractures of hips and elbows as well as camptodactyly were present. There were rocker-bottom feet with bilateral varus deformities. Micrognathia with "carp mouth" appearance was seen. The lungs weighed a total of 12.9 gm (expected weight 38 gm). The lung/body weight ratio was 0.008 (normal >0.012). The radial alveolar count was 2.5 (normal 3.6). The central nervous system was not studied in detail. The remaining viscera were normal. Pancreatic islet cell hyperplasia was not present.

Case 2. The same patient was examined in the twenty-sixth week of her second pregnancy. Ultrasound findings indicated a single fetus with estimated weight of 740 gm (twentieth percentile). Other evidence of growth retardation was a femur length in the fifth percentile. Polyhydramnios was present. There was ulnar deviation of a hand and a rocker-bottom foot. No extension of fingers was observed. Knees were fixed in flexion. Facial features included micrognathia and a depressed nasal tip. Fetal breathing movements were absent during 90 minutes of observation. These findings were highly suggestive of a recurrence of the syndrome.

She was again referred for consultation at thirty-six

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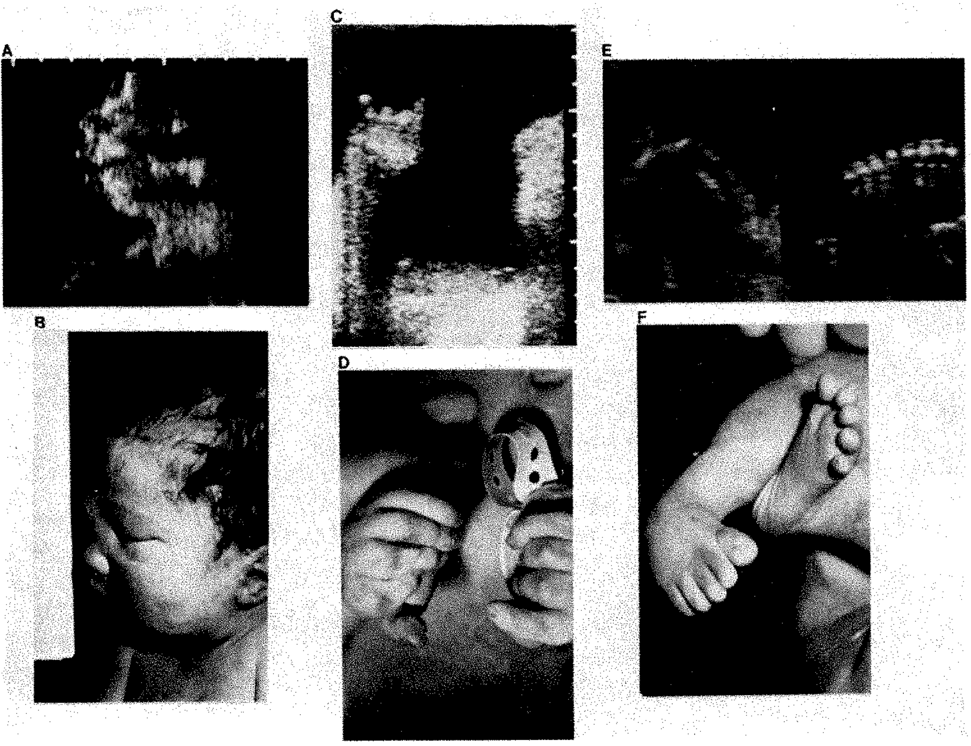

Fig. 1. Case 2. *A*, Ultrasound profile of face. Flattened nasal bridge and micrognathia are apparent. *B*, Postmortem photograph of face. Note the low-set ear and micrognathia. *C*, Ultrasonogram showing increased amniotic fluid, elbow held in flexion, and camptodactyly. *D*, Postmortem photograph of hand fixed in flexion. Compare with *C*. *E*, Ultrasonogram. On left is a foot with the knee fixed in flexion and appearance of "rocker bottom." On right are two fists which remained in this attitude for 90 minutes. *F*, Postmortem photograph. Note the clubbing of the right foot and the absence of skin creases on the left foot.

weeks' gestation for the sudden increase in abdominal size. Polyhydramnios was clinically obvious and confirmed by ultrasound. Previous ultrasound findings were confirmed; in addition, a deformed ear, clubfoot, small thorax, camptodactyly, definite micrognathia, and no fetal respirations were noted (Fig.1, *A*, *C*, and *E*).

The baby was delivered by elective repeat cesarean section at 36 weeks' gestation and lived only 1 hour. The female infant weighed 2260 gm. The umbilical cord was short but not as dramatically noticeable as in the previous pregnancy.

Autopsy report. Hypertelorism, epicanthal folds, low-set malformed ears, depressed nasal tip, small down-turned mouth, high arched palate, micrognathia, ulnar deviation of hands, camptodactyly, absent distal palmar creases, rocker-bottom feet with ankylosis, and ankyloses of both hips were reported on autopsy (Figs. 1, *B*, *D*, and *F*, and 2).

The combined weight of the lungs was 26 gm (expected normal weight 44 gm). Lung/body weight ratio was 0.012 (normal >0.012). Radial alveolar count was 4.0 (expected normal 4.5). Other findings of note were pancreatic islet cell hyperplasia and fat necrosis as well as acute focal inflammation of the lower abdominal wall. Neuropathologic study revealed no gross or histologic abnormalities of the brain or spinal cord.

Comment

Thirty-one cases of the Pena-Shokeir syndrome, including the two described in this paper, have now been reported. Table I summarizes the salient features of the syndrome and the noted incidence of each.

Obstetric considerations

Polyhydramnios. The patient described was originally referred for prenatal diagnosis because polyhydramnios was present. Although polyhydramnios is not a universal finding in Pena-Shokeir syndrome, it may be more frequent than reported, since obstetric records on many of the cases were incomplete. The occurrence of a variety of congenital anomalies and chromosomal disorders in patients with increased amniotic fluid volume is well known. A frequent cause for increased amniotic fluid volume is postulated to be obstruction of the passage of amniotic fluid through the fetal gastrointestinal tract. In Pena-Shokeir syndrome, impair-

Table I. Pena-Shokeir syndrome

Characteristic	*Reported frequency*
Obstetric features	
Growth retardation	28/30
Polyhydramnios	18/28
Short umbilical cord	6/7
Perinatal death	27/31
Pulmonary hypoplasia	29/31
Dysmorphology face	
Hypertelorism	27/29
Low-set deformed ears	30/30
Depressed tip of nose	25/26
Micrognathia	29/29
Dysmorphology of extremities	
Camptodactyly	28/30
Hyoplastic dermal ridges/creases	15/16
Clubfoot or rocker-bottom foot	27/29
Arthrogryposis	31/31
Male infants	14
Female infants	17
Cryptorchidism	14/14

ment of fetal swallowing has been suggested as the likely cause of polyhydramnios.[16] The facial deformities, especially the small mouth, may be contributory. No other site of gastrointestinal stenosis or atresia was present in our cases. Almost all the reported cases of Pena-Shokeir syndrome manifested varying degrees of growth retardation.

Short umbilical cord. Avulsion of the umbilical cord from the abdomen of the newborn infant during delivery by cesarean section certainly must be a rare occurrence and dramatically demonstrates how short the cord must have been. Miller et al.[17] identified common factors in newborn infants with short umbilical cords. These are early intrauterine constraint and gross structural or limb defects that limit intrauterine movement. A variety of examples of limb dysfunction included arthrogryposis and the Pena-Shokeir syndrome.

Moessinger et al.[18] provided experimental evidence that in rats, reduction of the amniotic fluid volume by amniocentesis with resultant oligohydramnios produced short umbilical cords. Paralysis of rat fetuses with curare also resulted in short umbilical cords. It seems likely that normal fetal body activity is a requisite for the umbilical cord to reach its normal length and that any interference with such activity early in pregnancy may lead to a short cord.

Pulmonary hypoplasia. The Pena-Shokeir syndrome is usually lethal during the first few days of life. The most frequent cause of death is pulmonary hypoplasia. Four infants that survived longer than 1 month have been described; they presumably had lesser degrees of lung hypoplasia.[2, 3, 10, 13]

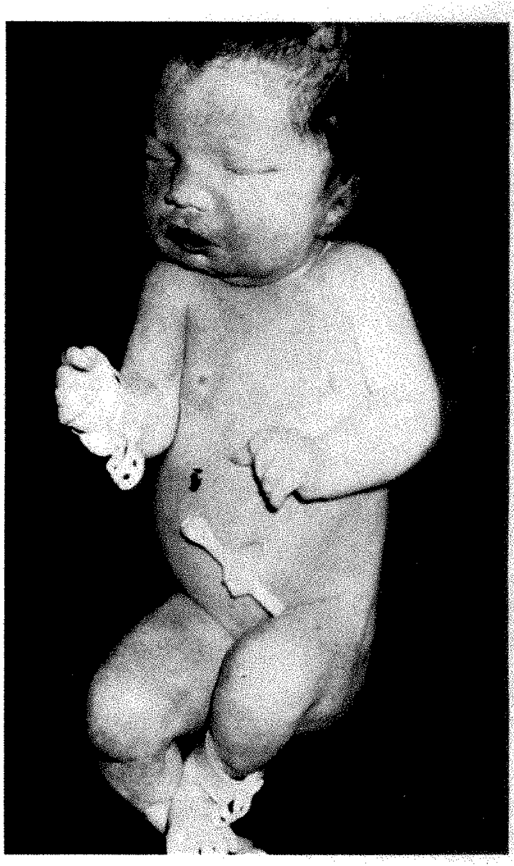

Fig. 2. Case 2, postmortem photograph. This view demonstrates hypertelorism, micrognathia, small mouth, limb deformities, and small thorax. In Case 1, the baby had an identical appearance.

Whenever pulmonary hypoplasia is diagnosed, it is usually accompanied by extrathoracic compression, thoracic cage compression, or intrathoracic compression.[19] The most common cause of extrathoracic compression is oligohydramnios associated with impared renal function or renal agenesis or associated with prolonged amniotic fluid leakage. Another well-known association is that of diaphragmatic hernia with lung hypoplasia. A number of cases of primary lung hypoplasia in the absence of other anomalies have been reported. The Pena-Shokeir syndrome is unique in that the lung hypoplasia occurs along with increased amniotic fluid volume.

No single definition for hypoplasia of the lungs is universally accepted. An incomplete list of methods for assessing lung development includes lung weight for a given gestational age, lung weight for a given body weight, lung weight/body weight ratio,[20] and radial alveolar counts.[21] Measurement of lung weight is influenced by the amount of fluid in the lungs. Ratios are influenced by the degree of somatic growth retardation present. Radial alveolar counts, properly performed, will give information about arrest of alveolar development. In our patients, absolute lung weight as well as lung weight/body weight ratios were below normal. The radial alveolar counts (not previously recorded in Pena-Shokeir syndrome) were below normal but were relatively less affected than the lung weights.

Facies. The facial features of Pena-Shokeir syndrome are listed in Table I. Intubation of newborn infants with Pena-Shokeir syndrome may be extremely difficult because of their small mouths, rigid jaws, and narrow upper airways. The described facial deformities may be due to limitation of motion of the facial musculature, secondary to mechanical or neurological impairment.

Extremities. Deformations of the limbs, also a component of Pena-Shokeir syndrome, are present whenever oligohydramnios is significant. These deformations are usually attributed to the restricted space for joint movement in utero leading to contractures. The increased volume of amniotic fluid in Pena-Shokeir syndrome would make this explanation untenable. Absence of skin creases in the palms and webbing indicate very early onset of deformations. The Pena-Shokeir syndrome is a specific disorder, one feature of which is arthrogryposis.

Other anomalies. Cryptorchidism is universally present in males. Other anomalies are occasionally seen, but no organ system is predominantly involved.

Genetic aspects. The Pena-Shokeir syndrome occurs in both male and female infants. Five sets of siblings with Pena-Shokeir syndrome have been reported. Consanguinity was present in four families. Couples with affected children also have had normal offspring. Family pedigree investigations support an autosomal recessive inheritance.

Etiology. Clinical observations and, more recently, an experimental model indicate that fetal akinesia may be responsible for all the manifestations of the Pena-Shokeir syndrome.[10, 16] One pathway leading to fetal akinesia is absence of amniotic fluid; this has been discussed in relation to the facial anomalies, short umbilical cord, and arthrogryposis as well as pulmonary hypoplasia. A second mechanism for production of fetal akinesia is neurological or muscular disease of the fetus. In five cases of the Pena-Shokeir syndrome, degeneration of the anterior horn cells has been noted on neuropathologic examination. An additional four newborn infants had atrophic degeneration of skeletal muscle in the absence of central nervous system disease. The majority of cases reported that had postmortem study of the nervous system did not have any lesions described. In our two patients, autopsy disclosed no evidence of brain or spinal cord disease. The Pena-Shokeir syndrome is thus not a homogeneous syndrome but probably has a variety of etiologic mechanisms.

There is mounting experimental evidence in animals that fetal breathing movements are essential for normal lung development.[22] Absence of fetal breathing leads to severe degrees of pulmonary hypoplasia. It is our opinion that a valid diagnosis of Pena-Shokeir syndrome must include some degree of pulmonary hypoplasia; if it is absent, another related member of the arthrogryposis complex would be a better diagnosis.

Fetal akinesia is an attractive concept because it can explain all the findings in the Pena-Shokeir syndrome, including the limb abnormalities, the facies, polyhydramnios, and the short umbilical cord.

After Brenholz et al.[3] suggested that the pancreatic islet cell hyperplasia might play a role in neuron damage, we reexamined the pancreases in our cases. Patient 1 had normal islets; Patient 2 had marked hyperplasia of the pancreatic islets.

Ultrasound and prenatal diagnosis. Chen et al.[4] described the ultrasound findings in a fetus subsequently proved to have the Pena-Shokeir syndrome at 32 weeks' gestation. Their findings included polyhydramnios, retrognathia, and flexion deformities of the extremities.

Ultrasound examination was performed in both our cases; the mother was reluctant to have an examination performed in the second pregnancy until 26 weeks of gestation. With knowledge of the nature of Pena-Shokeir syndrome, this examination was more directed than the one performed during the first pregnancy. The facial features of the syndrome, including micrognathia, low-set ears, and deformed nose as well as arthrogryposis and camptodactyly, were clearly identified. Rocker-bottom feet were seen. Polyhydramnios and intrauterine growth retardation were confirmed. Of some importance is the fact that on all three examinations performed, fetal respiratory activity was absent. This was true during an observation period of 90 minutes. The absence of fetal breathing movements, which can usually be observed as early as 16 weeks' gestation, may be the clue to early prenatal diagnosis. If such a diagnosis can be accomplished earlier in pregnancy, it would provide the couple with the option of termination. The presence of breathing movements and active limb motion would indicate a normal fetus if none of the other stigmata of the syndrome could be identified by ultrasound.

Early performance of an ultrasound examination with study of the range of limb movements might also be helpful in diagnosis. As indicated by our examinations, camptodactyly and limited movement of joints as well as foot deformities are well advanced by the twenty-sixth week of pregnancy. Markedly increased amniotic fluid volume may occur relatively late in the course of the syndrome, although the amniotic volume was moderately increased at 26 weeks. Case 2 represents the first prenatal diagnosis of the Pena-Shokeir syndrome. Earlier prenatal diagnosis may be possible.

Many instances of arthrogryposis are not lethal, do not have lung hypoplasia as a component, and must be distinguished from the Pena-Shokeir syndrome. Presumably, normal fetal breathing movements would be observed on ultrasound examination. The facial anomalies and the hand and foot abnormalities are present in trisomy 18, and therefore karyotyping of amniotic fluid cells to rule out this disorder might be useful, although trisomy 18, like Pena-Shokeir syndrome, is usually lethal during the early neonatal period.

In summary, two siblings with lethal Pena-Shokeir syndrome have been reported. The ultrasound and obstetric features of this syndrome have been reviewed. In the second case, prenatal diagnosis of this rare syndrome has been described for the first time. If the absence of fetal respirations proves to be a consistent observation, then earlier prenatal diagnosis is possible.

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Arrested puberty associated with a Sertoli-Leydig cell tumor

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Androgen-producing ovarian tumors are rarely recognized as a cause of delayed or arrested puberty, despite their frequent association with secondary amenorrhea in the older patient. A case is discussed of a Sertoli-Leydig cell tumor in an 18-year-old girl resulting in arrest of breast development and primary amenorrhea. (AM J OBSTET GYNECOL 1985;152:308-9.)

Key words: Sertoli-Leydig cell tumor, arrested puberty

Functional ovarian tumors are generally recognized as a cause of pseudo–precocious puberty. Androgen-producing ovarian tumors, although frequently associated with secondary amenorrhea, have rarely been reported as a cause of delayed or arrested pubertal development. The following case is an example of arrested pubertal development due to a functional Sertoli-Leydig cell tumor.

Case report

The patient, a 17½-year-old nulligravid girl, presented with primary amenorrhea and a 1-year history of clitoromegaly and deepening voice. Breast development began at age 13 but then failed to progress fully. Pubic hair began to develop at age 12 and progressed normally. She had no excessive hair growth or temporal balding. Her past medical history was unremarkable and she denied the ingestion of any medications. The patient's one older sister and mother both experienced normal puberty and menarche. On physical examination, the patient was 69 inches tall and weighed 118 pounds. She was muscular in appearance and had a male body habitus and a husky voice. No hirsutism or temporal balding was noted; mild facial acne was present. Breast development had reached a Tanner stage III and no galactorrhea could be demonstrated. The abdomen was free of masses. Pelvic examination revealed a female escutcheon (Tanner stage V) and a clitoris enlarged to 4 by 1.5 cm. The vagina was poorly rugated; the uterus was small and there was a suspicion of a right adnexal mass. Pelvic sonogram confirmed the presence of a solid right ovarian neoplasm measuring 6 cm in diameter. The initial hormonal evaluation included a testosterone level of 390 ng/dl (normal 19 to 120), a 17-hydroxyprogesterone level of 485 ng/dl (normal 10 to 280), and androstenedione level of 382 ng/dl (normal 70 to 310), and an estradiol level of 32 pg/ml (normal 10 to 500).

With the presumptive diagnosis of an androgen-producing ovarian tumor, the patient underwent an exploratory laparotomy. An intact neoplasm of the right ovary measuring 6 cm was found. The left ovary appeared normal and biopsy of that ovary had been refused. A right oophorectomy was performed. Pathologic examination documented a Sertoli-Leydig cell tumor. After operation the androgen levels fell rapidly, with normal testosterone, androstenedione, and 17-hydroxyprogesterone levels noted on the first postoperative day; the levels remained normal at her 7-week visit. The patient did well and had her first menses 6 weeks postoperatively. At her 5-month visit, she reported the occurrence of menses at monthly intervals and the return of a feminine voice, but she had not yet reached a Tanner stage IV of breast development.

Comment

Ovarian neoplasms are rare in children and adolescents. Norris and Jensen,[1] in reviewing the experience at the Armed Forces Institute of Pathology, found 353 patients under the age of 20 with a primary ovarian tumor. This represented only 6% of their total number of ovarian neoplasms. Although Sertoli-Leydig cell tumors, also known as arrhenoblastomas, are the most common virilizing ovarian tumors, they comprise less than 1% of all ovarian tumors and hence are extremely rare in children. The mean age for the occurrence of this neoplasm is 34 years, although it has been diagnosed at all ages. Norris and Jensen[1] in their review noted 14 cases in girls under 20 years, only two of which were discovered prior to puberty. Approximately 75% present with signs of virilization and there is less than a 5% incidence of bilaterality. Sertoli-Leydig cell tumors have been reported as a cause of heterosexual precocious puberty. The increased androgen production from these neoplasms may lead to secondary amenorrhea in the postmenarchal woman. A similar effect on the hypothalamic-pituitary-ovarian axis might also be expected in the pubertal girl, leading to an arrest

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of further pubertal development. An analogous situation would be the case of untreated congenital adrenal hyperplasia, where excessive androgen levels of adrenal origin have been associated with delayed puberty. Several cases of Sertoli-Leydig cell tumors have been reported in association with primary amenorrhea. In 1973, Brant[2] reported a case of an arrhenoblastoma in a 12-year-old girl who presented with primary amenorrhea, acne, hirsutism, clitoromegaly, and deepening voice. The stage of pubertal development was not specified and no steroid levels were included. No postoperative menstrual function was reported. In the same year, Mahran and Iskander[3] reported a case of gynandroblastoma, an ovarian tumor composed of both Sertoli-Leydig cell and granulosa cell components. This 22-year-old woman presented with primary amenorrhea; she was described as having poorly developed breasts and hypoplastic uterus and ovaries. Again, the stage of pubertal development, steroid levels, and postoperative follow-up were not included.

The case reported here is interesting in that the tumor's testosterone secretion reached a critical level after puberty had already begun, apparently just prior to menarche and at a Tanner stage III of breast development. Once the testosterone level decreased to the normal range after operation, menarche occurred and further progression through pubertal development is expected.

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Long-term survival rates with various chemotherapeutic regimens in Stages III and IV ovarian adenocarcinoma

The influence of optimum pretreatment surgical resection

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This report compares long-term survival rates for patients treated with four different chemotherapeutic regimens for Stages III and IV ovarian adenocarcinoma. The patients were entered into consecutive, prospective, randomized studies with an essentially common chemotherapeutic arm. The first study compared the single agent melphalan with actinomycin D, 5-fluorouracil, and Cytoxan. The second study compared 5-fluorouracil plus Cytoxan and methotrexate–leucovorin rescue plus Cytoxan. The patient characteristics in the two studies were very similar except for more aggressive tumor-reductive operations in the second study. Observed survival rates for the first 2 years in the second study were very much higher than in the first study. However, by the third, fourth, and fifth years, the survival rates of the 5-fluorouracil–Cytoxan–treated individuals had reached the same low levels seen in the first study. It appears that an optimum surgical procedure by itself may enhance survival during the first 2 years. Survival with methotrexate–leucovorin rescue plus Cytoxan was statistically significantly better than with melphalan or actinomycin D–5-fluorouracil–Cytoxan. Third-, fourth-, and fifth-year survival rates with methotrexate–leucovorin rescue plus Cytoxan were substantially higher than with 5-fluorouracil–Cytoxan; however, the survival distributions for these two treatments were not statistically significantly different. Long-term survival rate data for patients with Stages III and IV ovarian adenocarcinomas treated with chemotherapy are rare. The 19% 5-year survival rate with methotrexate–leucovorin rescue plus Cytoxan in the present study is considerably higher than other reported survival rates. (AM J OBSTET GYNECOL 1985;152:310-4.)

Key words: Long-term survival, ovarian cancer, chemotherapy

Ovarian adenocarcinoma is one of the most chemoresponsive of the solid tumors and in recent years chemotherapy has emerged as the preferred postsurgical treatment for Stages III and IV ovarian adenocarcinoma. However, despite the increasingly high initial response rates with recent combination chemotherapy, patients' long-term survival rates have not been demonstrably improved. The literature contains abundant information concerning tumor chemoresponsiveness and short-term patient survival, but there are very little data relating to long-term survival.

Two of our previously reported prospective, randomized chemotherapy trials in Stages III and IV ovarian adenocarcinoma have now reached the point where all patients have been observed either to death or for a minimum of 5 years. These were consecutive studies that, in addition, had an essentially common chemotherapeutic arm. The purpose of the present report is to compare long-term survival of patients on these chemotherapeutic regimens and to examine possible prognostic factors contributing to long-term survival.

Material and methods

The first of the two studies, carried out between 1971 and 1975, compared the single agent melphalan with the combination actinomycin D, 5-fluorouracil, and Cytoxan.[1] One hundred eight patients were entered, 54 in each chemotherapeutic arm of the study. The second study compared the efficacy of the combination high-dose methotrexate–leucovorin rescue plus Cytoxan with 5-fluorouracil plus Cytoxan.[2] Twenty-three patients were randomized to each of these chemotherapeutic regimens. The second study was carried out between 1976 and 1978. Both studies were conducted by the same investigators, and the same pathologist examined all the pathologic material. All patients had histologically proved International Federation of Gynaecology and Obstetrics Stage III or IV epithelial ovarian cancers that were serous, mucinous, undifferentiated adenocarcinomas or other. All patients had had no prior therapy other than operation.

In the first study, single-agent Melphalan was given

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Table I. Characteristics of patients with Stages III and IV ovarian adenocarcinoma treated in consecutive randomized trials

	Treatment			
	First study		*Second study*	
	AC-FUCY	*Melphalan*	*FUCY*	*MECY*
Total No. of evaluable patients	47	49	22	21
Mean (yr)	55.7 (38-80*)	51.8 (27-72)	57 (30-81)	55 (11-78)
Stage				
III	36	37	17	17
IV	11	12	5	4
Histologic features				
Serous	35	36	18	17
Mucinous	5	5	2	1
Undifferentiated adenocarcinoma	5	4	1	2
Other	2	4	1	1
Histologic differentiation				
Well differentiated	3	1	2	2
Moderately differentiated	26	33	11	8
Poorly differentiated	18	15	9	11
Operation				
Biopsy only, <25%	20 (43%)	22 (45%)	5 (23%)	3 (14%)
Tumor-reductive, ≥50%	17 (36%)	20 (41%)	14 (64%)	18 (86%)
Residual tumor after operation				
>2 cm	43	45	17	13
<2 cm	3 (6%) 1 Unknown	4 (8%)	5 (23%)	8 (38%)

AC-FUCY = Actinomycin D, 5-fluorouracil, and Cytoxan; FUCY = 5-fluorouracil and Cytoxan; MECY = methotrexate–leucovorin rescue plus Cytoxan.

in a dosage of 0.2 mg/kg/day in divided doses for 5 days for a total dose of 1 mg/kg per 5-day cycle. The cycle was repeated every 4 weeks if blood counts were adequate. The treatment regimen with actinomycin D–5-fluorouracil–Cytoxan was 0.5 mg of actinomycin D, 8 mg/kg of 5-fluorouracil, and 7 mg/kg of Cytoxan. All three agents were given intravenously for 5 days. The 5-day cycle was repeated every 4 weeks if blood counts were adequate. In the second study the methotrexate–leucovorin rescue plus Cytoxan regimen consisted of 750 mg/M^2 of methotrexate administered as a 4-hour intravenous infusion. Six hours after the completion of the methotrexate infusion, administration of leucovorin rescue was begun at a dosage of 10 mg/M^2 intramuscularly every 6 hours for 12 doses. In addition, each patient received 250 mg/M^2 of Cytoxan intravenously per day for 5 days beginning on the day of the methotrexate infusion. Courses of treatment were repeated every 4 weeks, provided that blood cell recovery was adequate. The 5-fluorouracil–Cytoxan regimen consisted of 280 mg/M^2/day of intravenous 5-fluorouracil for 5 days plus 250 mg/M^2/day of intravenous Cytoxan for 5 days. Courses of 5-fluorouracil–Cytoxan were repeated every 4 weeks if blood cell recovery was adequate.

The actinomycin D–5-fluorouracil–Cytoxan chemotherapeutic arm of the first study and the 5-fluorouracil–Cytoxan arm of the second study are considered to be common. The only difference between the two regimens was the exclusion of actinomycin D in the second study. It was dropped because it contributed substantially to toxicity and was not known to be active by itself in this disease.

In these studies "biopsy only" is defined as <25% resection of tumor volume, and "tumor reduction" is defined as resection of ≥50% of the tumor volume.

Statistical methods. The duration of survival was calculated with the first day of chemotherapy used as day 1. Estimated survival distributions were calculated by the method of Kaplan and Meier.[3] Comparisons of survival distributions were performed with Cox's regression model.[4] All p values are one-sided; comparisons with $p < 0.05$ were considered to be statistically significant.

Results

Table I depicts the patient characteristics for all evaluable patients in each of the two studies. Patients were considered evaluable if they received one or more courses of chemotherapy and were reexamined at least once after chemotherapy. The studies were quite comparable with respect to patient age, stage of disease, histologic features, and histologic differentiation. The only factors that were obviously different were the extent of the operation performed and the amount of residual tumor after operation. In the 5-fluorouracil–

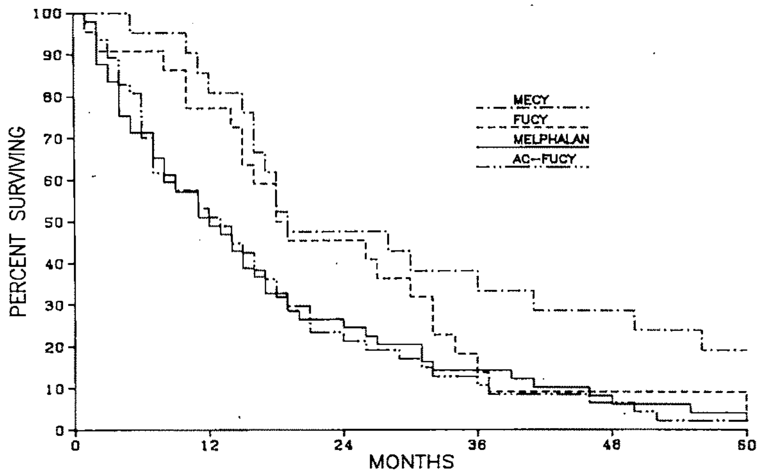

Fig. 1. Survival by chemotherapeutic *MECY* = Methotrexate-leucovorin plus Cytoxan; *FUCY* = 5-fluorouracil plus Cytoxan; *AC-FUCY* = actinomycin D and 5-fluorouracil plus Cytoxan.

Table II. Comparison of survival for each treatment regimen

	No. surviving and estimated survival rates							
	MECY (*n* = *21*)		*FUCY* (*n* = *22*)		*AC-FUCY* (*n* = *47*)		*Melphalan* (*n* = *49*)	
Years	*n*	%	*n*	%	*n*	%	*n*	%
1	17	81	17	77	24	51	25	51
2	10	48	10	46	10	21	13	27
3	8	38	4	18	6	13	7	14
4	6	29	2	9	3	6	3	6
5	4	19	2	9	1	2	2	4

One-sided p value (from Cox's[4] proportional hazards model): MECY versus FUCY, 0.12; MECY versus AC-FUCY, 0.004; MECY versus melphalan, 0.003; FUCY versus AC-FUCY, 0.06; FUCY versus melphalan, 0.08.

Cytoxan and methotrexate–leucovorin rescue plus Cytoxan study, tumor reduction was emphasized, and whenever possible there was an attempt to reduce the residual tumor so that no single tumor mass was >2 cm.

Table II lists and compares the survival data for each regimen. The same data are plotted in Fig. 1. The observed survival rates of patients treated in the first study with either melphalan or actinomycin D–5-fluorouracil–Cytoxan were remarkably similar and the curves are virtually superimposable. Both therapies had 51% survivors at the end of 1 year; 27% and 21%, respectively, after 2 years; 14% and 13%, respectively, at 3 years; 6% each at 4 years; and 4% and 2%, respectively, at 5 years.

Also listed in Table II and plotted in Fig. 1 are similar survival data for patients treated with methotrexate–leucovorin rescue plus Cytoxan or 5-fluorouracil–Cytoxan. The first point of interest is the substantially higher 1- and 2-year survival rates observed for patients treated with methotrexate–leucovorin rescue plus Cytoxan or 5-fluorouracil–Cytoxan as compared to those with actinomycin D–5-fluorouracil–Cytoxan or melphalan. Eighty-one percent and 77%, respectively, of patients treated with methotrexate–leucovorin rescue plus Cytoxan or 5-fluorouracil–Cytoxan were alive at the end of 1 year. At the end of 2 years, 48% and 46%, respectively, had survived. This compares with 51% surviving 1 year and 21% or 27% for 2 years with actinomycin D–5-fluorouracil–Cytoxan or melphalan. The patients treated with 5-fluorouracil–Cytoxan had higher observed 2-year survival rates than those treated with actinomycin D–5-fluorouracil–Cytoxan despite a higher initial response rate with actinomycin D–5-fluorouracil–Cytoxan.[1, 2] From the third year on, survival rates for patients receiving 5-fluorouracil–Cytoxan, melphalan, and actinomycin D–5-fluorouracil–Cytoxan were essentially the same. As noted in Table I, the only apparent differences in patient characteristics between the actinomycin D–5-fluorouracil–Cytoxan and 5-fluorouracil–Cytoxan groups were in the extent of the operations performed and the amount of resid-

Table III. Characteristics of long-term survivors: Methotrexate–leucovorin rescue plus Cytoxan versus 5-fluorouracil and Cytoxan

Patient	*Age*	*Stage*	*Histology*	*Grade*	*Tumor reduction (%)*	*Residual disease (cm)*	*Survival (mo)*	*Status*	*Therapy*
1	11	III	Serous	Moderate	>75	<2	74+	Alive with disease	MECY
2	56	III	Serous	Moderate	>75	<2	66+	Alive, NED	MECY
3	39	III	Serous	Well	98	<2	76+	Alive, NED	MECY
4	55	III	Endom.	Poor	>75	>2	62	Died of disease	MECY
5	50	III	Adeno.	Poor	50	>2	51	Died of disease	MECY
6	30	III	Serous	Moderate	95	<1	56	Died of disease	MECY
7	41	IV	Serous	Moderate	>75	<1	41	Died of disease	MECY
8	57	III	Serous	Poor	50	>2	38	Died of disease	MECY
9	69	III	Serous	Moderate	90	<2	70+	Alive, NED	FUCY
10	58	III	Serous	Moderate	65	>2	63	Died of disease	FUCY
11	55	III	Serous	Moderate	90	>2	37	Died of disease	FUCY
12	71	IV	Serous	Moderate	40	>2	36	Died of disease	FUCY

ual tumor after operation. Forty-three percent of the actinomycin D–5-fluorouracil–Cytoxan group and 23% of the 5-fluorouracil–Cytoxan group had only biopsies of the tumor. Thirty-six percent of patients in the actinomycin D–5-fluorouracil–Cytoxan group, as compared with 64% of patients in the 5-fluorouracil–Cytoxan patients, had tumor reduction. Six percent of patients in the actinomycin D–5-fluorouracil–Cytoxan group and 23% in the 5-fluorouracil–Cytoxan group had small residual tumor masses after operation.

The third-, fourth-, and fifth-year survival rates in the patients treated with methotrexate–leucovorin rescue plus Cytoxan were substantially higher than those for any of the other regimens. In addition, patients receiving methotrexate–leucovorin rescue plus Cytoxan had statistically longer survival times than patients treated with actinomycin D–5-fluorouracil–Cytoxan or melphalan (see Table II for p values). The methotrexate–leucovorin rescue plus Cytoxan regimen gave 3-, 4-, and 5-year survival rates of 38%, 29%, and 19%, respectively.

One might conclude from comparisons of the characteristics and the survival rates of patients receiving 5-fluorouracil–Cytoxan and actinomycin D–5-fluorouracil–Cytoxan that surgical aggressiveness in the 5-fluorouracil–Cytoxan group accounted for the enhanced observed 2-year survival rate.

Table III details some of the characteristics of the long-term survivors (≥3 years) in the methotrexate–leucovorin rescue plus Cytoxan/5-fluorouracil–Cytoxan study. Of the long-term survivors treated with 5-fluorouracil–Cytoxan, only Patient 9 of the five patients listed in Table I who had residual tumor of ≤2 cm was a long-term survivor. This percentage (20%) of long-term survivors treated with 5-fluorouracil–Cytoxan and with small residual tumors did not differ from the 18% (three of 17) of patients who were long-term survivors with residual nodules of >2 cm. In contrast, five of eight (63%) patients listed in Table I with small residual tumors treated with methotrexate–leucovorin rescue plus Cytoxan survived ≥3 years, whereas only three of 13 (23%) patients with residual tumor masses >2 cm, also treated with methotrexate–leucovorin rescue plus Cytoxan, survived for ≥3 years. The correlations between long-term survival and small residual tumor were inconsistent.

Comment

These two consecutive, prospective, and randomized chemotherapeutic trials, with an essentially common chemotherapy arm, offer a good opportunity to study some of the factors contributing to long-term survival in patients treated for ovarian adenocarcinoma.

It is generally agreed that tumor reduction is a positive factor in prolonging survival if all remaining tumor masses are ≤2 cm in diameter. The present data indicate that survival can be enhanced by aggressive tumor reduction in combination with methotrexate–leucovorin rescue plus Cytoxan. However, survival beyond 2 years does not appear to be influenced by the extent of the initial operation. The substantially better 3- to 5-year survival rates in the methotrexate–leucovorin rescue plus Cytoxan group appear to be a consequence of the improved chemotherapeutic efficacy of the regimen rather than of any other observed variable.

Since there are presently several new chemotherapeutic regimens with high-response rates available to treat patients with ovarian carcinomas, we must look beyond the response rates and assess the therapies in terms of long-term survival. The present study indicates that aggressive tumor reduction by itself may be able to lengthen survival during the first 2 years. This suggests that it may take more than 2 years of observation, in patients with optimal operations, to separate the effects of tumor reduction from chemotherapeutic efficacy.

Reports of long-term survival rates in patients with Stages III and IV ovarian adenocarcinomas treated with chemotherapy are rare. Two large trials reported <10% 5-year survival.[5, 6] A recent report from one of the same institutions presented 4-year survival rates in a randomized study of a variety of single-agent and multiple-agent chemotherapeutic regimens.[7] The overall patient survival rate was 24% at 4 years. Of these surviving patients, 45% had clinically demonstrable residual disease. No individual single- or multiple-agent regimen appeared to be superior. A 4-year survival rate of 25% has been reported for the popular combination of cisplatin, Adriamycin, and Cytoxan.[8] The 29% 4-year survival rate with methotrexate–leucovorin rescue plus Cytoxan in the present study is comparable.

The survival rates with methotrexate–leucovorin rescue plus Cytoxan are statistically significantly better than those with single-agent melphalan or multiple-agent actinomycin D–5-fluorouracil–Cytoxan. The 19% 5-year survival rate, although modest, is to our knowledge the highest 5-year survival rate reported for advanced stages of this disease.

In a more recent study an alternating chemotherapeutic regimen consisting of weekly cisplatin and monthly courses of methotrexate–leucovorin rescue plus Cytoxan has proved significantly better than methotrexate–leucovorin rescue plus Cytoxan alone in producing negative second-look laparotomies[9] and therefore promises to increase the long-term survival rate above that achieved in this report with methotrexate–leucovorin rescue plus Cytoxan alone.

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Effect of treatment with sodium valproate on plasma adrenocorticotropic hormone and cortisol concentrations in pregnancy

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To investigate whether treatment with valproic acid in pregnancy decreases adrenocorticotropic hormone and cortisol secretion, we measured their concentrations in maternal and umbilical cord blood from a patient receiving valproic acid. We found them to be normal. Valproic acid may not decrease adrenocorticotropic hormone/cortisol levels in pregnant patients or their fetuses. (AM J OBSTET GYNECOL 1985;152:315-6.)

Key words: Valproic acid, pregnancy, adrenocorticotropic hormone, cortisol, fetus

Valproic acid is a relatively new antiepileptic drug. During pregnancy, its use has been associated with an increase in the incidence of spina bifida and other neural tube defects. In addition, it has been shown that valproic acid increases γ-aminobutyric acid (GABA) brain concentrations. The latter may mediate the decrease in adrenocorticotropic hormone (ACTH) levels observed in adult patients with Nelson's syndrome.[1] Recently we had the opportunity to evaluate a patient who was being treated with valproic acid during pregnancy and in the intrapartum period. We measured maternal and fetal concentrations of ACTH and cortisol to answer the question whether this treatment decreases the concentrations of these two hormones in the fetal-maternal unit.

Case report

S. W. was a 26-year-old, gravida 1, para 0, black woman with a 13-year history of myoclonic epilepsy. Her symptoms were inadequately controlled by Dilantin and phenobarbital as well as by carbamazepine. On initiation of valproic acid therapy, the number of fits decreased. When the patient started taking 3000 mg of valproic acid a day and achieved therapeutic levels, she became seizure free.

Her prenatal course was essentially uncomplicated except for the seizures. For the last 3 months of her pregnancy, the only antiseizure medication she received was valproic acid. She was evaluated with semiweekly nonstress tests, which were reactive. She presented in spontaneous labor at term but required Pitocin augmentation. She was delivered spontaneously of a normal 7-pound, 7½ ounce male infant with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The patient's postpartum course and the baby's immediate neonatal course were uncomplicated. Subsequently the patient was lost to follow-up.

On the day of delivery the valproic acid level was 58 μg/ml (therapeutic range 50 to 100 μg/ml). ACTH and cortisol concentrations were measured by specific radioimmunoassays. In the immediate antepartum period, the ACTH concentrations were 57.8 to 66 pg/ml. During early labor the highest concentration was 161 pg/ml while, at the time of delivery, it was 103 pg/ml (normal value 194 ± 28.3 pg/ml). The umbilical arterial ACTH concentration was 86 pg/ml while the concentration of the umbilical vein was 172.6 pg/ml (normal value 143 ± 7 pg/ml). Maternal cortisol concentrations, measured at the same time as ACTH, included antepartum values of 270 to 412 ng/ml, intrapartum values of 780 ng/ml, and, at the time of delivery, values of 614 ng/ml (normal value 287 to 639 ng/ml). The umbilical arterial level was 206 ng/ml while the umbilical venous level was 147 ng/ml (normal values 88 to 300 ng/ml).

Comment

The mode of action of valproic acid is not known. However, treatment with this drug results in increased concentrations of GABA, an inhibitory central nervous system neurotransmitter, by decreasing GABA transaminase activity. GABA is involved in both corticosteroid hypothalamic feedback and the release of biologically active corticosteroid-releasing factor. Hence, in patients with elevated baseline ACTH levels, such as in Nelson's syndrome, treatment with valproic acid results

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in reduced plasma ACTH concentrations.[1] More recently, studies in children with seizure disorders[2] have suggested that treatment with valproic acid may result in an incomplete suppression of ACTH as well as cortisol levels from normal baselines.

To investigate whether these effects occur in the maternal-fetal unit, we measured ACTH and cortisol levels in both maternal venous plasma and umbilical arterial and venous plasma in a patient receiving long-standing treatment with valproic acid. In contrast to the previously published hormonal studies in children, where multiple anticonvulsants were used,[2] this patient was not receiving any other medications. The ACTH and cortisol levels in our patient were well within the normal range for normal parturients. Similarly, the umbilical arterial and umbilical venous plasma ACTH and cortisol levels were not different from those reported in normal patients. Thus it appears that sodium valproate therapy during pregnancy and delivery may not decrease ACTH and cortisol levels in the maternal and fetal compartment.

An extensive literature search did not yield any reports on the effects of sodium valproate therapy on ACTH and cortisol concentrations in normal pregnant patients or fetuses with normal baseline levels. Thus our observations represent the only instance in which these hormones have been measured in maternal-fetal plasma in this clinical setting.

Because of the potential teratogenicity and endocrine problems associated with sodium valproate therapy, its use during pregnancy should be restricted. If it is used, patients as well as their fetuses and neonates should be monitored closely for teratogenic effects as well as hormonal disturbances.

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Unsuccessful treatment of fetal immunologic thrombocytopenia with dexamethasone

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Corticosteroid therapy near term for mothers with immunologic thrombocytopenia has recently been suggested as a clinically useful method to prevent neonatal thrombocytopenia. The unreliability of this approach is illustrated by the case of an infant with a low platelet count delivered after the maternal administration of dexamethasone. (AM J OBSTET GYNECOL 1985;152:316-7.)

Key words: Thrombocytopenia, dexamethasone, neonate

Autoimmune thrombocytopenic purpura is caused by the production of an antiplatelet antibody and the subsequent destruction of platelets by the reticuloendothelial system. During pregnancy the maternal antiplatelet antibody can cross the placenta to produce fetal/neonatal thrombocytopenia, clinical bleeding, and increased risk of perinatal morbidity and mortality.

The administration of prednisone, 1 mg/kg/day, to pregnant women with autoimmune thrombocytopenic purpura produces a therapeutic response in the majority, and the platelet count usually rises within 3 to 7 days following initiation of treatment. It has been claimed that prednisone given to pregnant women during the last weeks of pregnancy prevents thrombocytopenia in the infant[1] but it has failed to do so in the experience of others.[2] However, dexamethasone and betamethasone have been suggested as better corticosteroids for this purpose, since placental transfer of those drugs results in a maternal/fetal concentration gradient of 1:1. In this report we describe the failure of maternal dexamethasone therapy to prevent thrombocytopenia in the infant.

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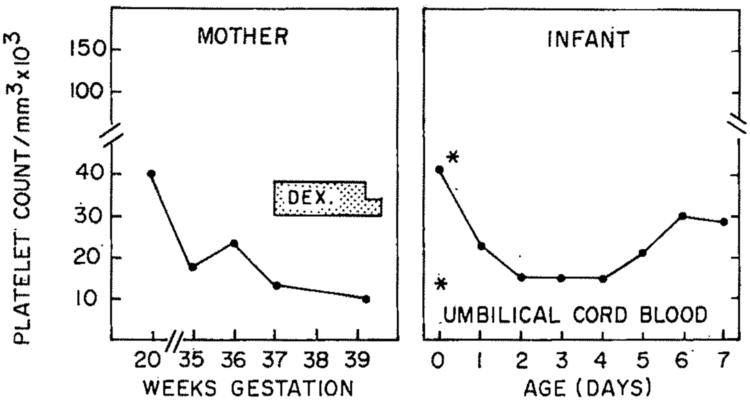

Fig. 1. Maternal and neonatal platelet counts.

Case report

S. L., a 21-year-old Oriental woman, was first seen at the Tri-Service General Hospital antenatal clinic in Taiwan at 20 weeks' gestation. A diagnosis of autoimmune thrombocytopenic purpura had been established at age 18 by bone marrow examination and elimination of other causes for her low platelet count. Because of a poor response to prednisone therapy, a splenectomy was performed at that time. During the next 3 years, her platelet count remained in the range of 50,000 to 100,000/mm^3 without any hemorrhagic symptoms.

Physical examination revealed a pregnant woman with scattered petechiae on the lower legs. Although the pregnancy progressed uneventfully, her platelet count remained low (Fig. 1). Therefore at 37 weeks' gestation dexamethasone, 4 mg/day by intramuscular injection (equivalent to 30 mg/day of prednisone), was started. After 15 days of dexamethasone injections, she presented at 39 weeks with ruptured membranes, and induction of labor was initiated with oxytocin. However, at a cervical dilatation of 3 cm two fetal scalp blood samples revealed platelet counts of 38,000/mm^3 and 49,000/mm^3. Therefore, the 2950 gm male infant was delivered by cesarean section; Apgar scores were 8 and 9 at 1 and 5 minutes. No excessive bleeding was encountered during surgery, and except for low platelet counts, both mother and infant had uneventful clinical courses. The neonatal platelet counts are shown in Fig. 1.

Comment

The rationale for corticosteroid therapy is based on the knowledge that these drugs increase the platelet count in patients with autoimmune thrombocytopenic purpura by suppressing Fc receptor function of macrophages, by impairing attachment and phagocytosis of the platelet-antibody complex, and perhaps by impairing antibody synthesis. If the corticosteroid crosses the placenta and enters the infant's circulation, splenic removal of the infant's platelets, which are coated by maternal antibody, might be prevented. Prednisone, which is pharmacologically inactive, undergoes hydroxylation in the liver to an active form, prednisolone. Both prednisolone and dexamethasone have 11-β OH radicals responsible for their physiologic activity. The placenta is a rich source of 11-β-ol-dehydrogenase and is capable of converting the active steroid to its inactive 11-keto form. Approximately 51% of prednisolone is converted to 11-keto compounds, but little conversion of dexamethasone occurs.

Nevertheless, the present case illustrates that maternal administration of dexamethasone cannot be relied upon to produce a normal fetal platelet count. It further confirms our contention that no antepartum maternal parameters safely predict the fetal platelet count.[2] If clinical decisions regarding the route of delivery are based on the fetal platelet count, then intrapartum fetal scalp blood sampling, despite technical problems in some patients, remains as the most dependable method.

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Current Development

Prostacyclin and thromboxane in gynecology and obstetrics

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The gynecologic and obstetric implications of the smooth muscle–relaxing, antiaggregatory prostacyclin and its endogenous antagonist, thromboxane A_2, are reviewed. In addition to the vascular wall and circulating platelets, which are primary sources for prostacyclin and thromboxane A_2, respectively, reproductive tissues produce great amounts of these prostanoids, evidently for the regulation of the vascular tone and/or vascular platelet interaction. Several gynecologic and obstetric disorders are characterized by abnormalities in prostacyclin and/or thromboxane A_2. In primary menorrhagia the uterine release of prostacyclin is increased, and consequently menstrual blood loss can be reduced with various prostaglandin synthesis inhibitors. Prostacyclin relaxes the nonpregnant myometrium in vitro and may also do so in vivo, although intravenous infusion of prostacyclin has no effect upon the uterine contractility in nonpregnant or pregnant subjects. Patients with pelvic endometriosis may have increased levels of prostacyclin and thromboxane A_2 metabolites in the peritoneal fluid. The prostacyclin/thromboxane A_2 balance shifts to thromboxane A_2 dominance in patients with gynecologic cancer. During pregnancy the production of prostacyclin and thromboxane A_2 increases in the mother and fetoplacental tissue. Preeclampsia and other chronic placental insufficiency syndromes are accompanied by prostacyclin deficiency in the mother and in fetomaternal tissues and by an overproduction of thromboxane A_2, at least in the placenta. These changes may account for the vasoconstriction and platelet hyperactivity, which are pathognomonic for hypertensive pregnancies. By directing the prostacyclin/thromboxane A_2 balance to prostacyclin dominance (by dietary manipulation, administration of prostacyclin and/or its analogues, drugs with prostacyclin-stimulating and/or thromboxane A_2-inhibiting action), it may be possible to prevent and/or treat hypertensive pregnancy complications in the future. (AM J OBSTET GYNECOL 1985;152:318-29.)

Key words: Menorrhagia, uterine contractility, hormones, cancer, preeclampsia

The so-called classical prostaglandins, the existence of which has been known for more than 50 years,[1] are of crucial significance in various fields of human reproduction.[2] They have also provided logical explanations for some gynecologic disorders, for instance, primary dysmenorrhea,[3] and consequently prostaglandin synthetase inhibitors are currently used for its treatment.[4] However, the role of classical prostaglandins is by no means as clear in many other gynecologic and obstetric disorders. Therefore, there was much interest aroused among gynecologists and obstetricians in the mid-1970s when two new prostanoids with potent actions on smooth muscle cells, thromboxane A_2[5] and prostacyclin (also called epoprostenol or prostaglandin I_2),[6] were discovered. It is now time, nearly a decade after their discovery, to summarize what has been learned about these prostanoids in gynecology and obstetrics.

Prostacyclin as cause of vasodilation and inhibitor of platelet aggregation

Prostacyclin, which was first identified from the vessel wall,[6] is chemically a bicyclic allylic ether prostaglandin.[7] Although endothelial cells produce the majority of the vascular prostacyclin, it can also be synthesized by other vessel wall components, such as smooth muscle cells[8] and even nonvascular tissues.[9] Prostacyclin, which is unstable in a buffer solution of physiologic pH (half-life 2 to 3 minutes), is hydrolyzed nonenzymatically to 6-keto-prostaglandin $F_{1\alpha}$ or metabolized enzymatically through 15-dehydrogenase to different metabolites[7, 10-12] (Fig. 1). It is not known, with certainty, how large a portion of prostacyclin is degraded through enzymatic and nonenzymatic pathways and whether this distribution changes in various physiologic conditions. In any case the measurements of these metabo-

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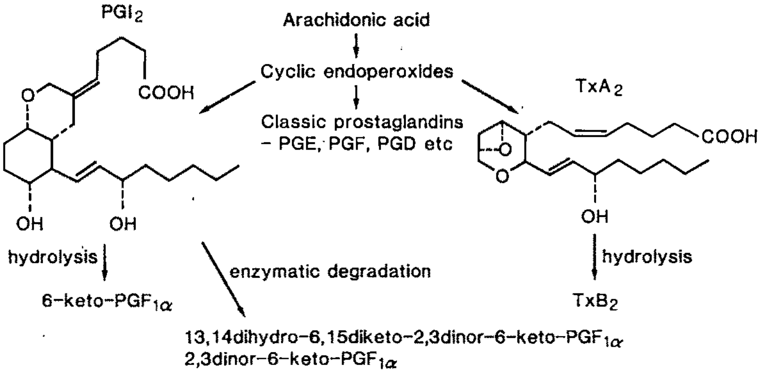

Fig. 1. Schematic pathways of prostacyclin *(PGI_2)* and thromboxane A_2 *(TxA_2)* biosynthesis and metabolism.

lites in plasma or urine have commonly been used for the assessment of prostacyclin synthesis in vivo. Prostacyclin was at first thought to be a circulating hormone,[13] but its presence in the circulation in physiologically significant concentrations has since been disputed.[11, 12, 14] This does not of course argue against the role of vascular wall prostacyclin in local vascular hemostasis.

Prostacyclin is the most potent inhibitor of platelet aggregation yet discovered, and it is also a potent vasodilator.[6] Other effects include a decrease in blood pressure, tachycardia, facial flushing,[15] stimulation of the renin-angiotensin-aldosterone axis,[16] and increases in blood glucose, glucagon, prolactin, and cortisol levels.[17] Since these data have been obtained by means of intravenous infusion of large doses of prostacyclin, it is possible that many of the changes involved may be pharmacologic rather than physiologic effects of prostacyclin.

Thromboxane as cause of platelet aggregation and vasoconstriction

Thromboxane A_2 is formed from cyclic endoperoxides through thromboxane synthetase, particularly in platelets,[5] and also in other tissues, including the vascular wall.[9] It differs in structure from the other prostaglandins in that the cyclopentane ring is replaced by a six-membered oxane ring (Fig. 1). Thromboxane A_2 induces platelet aggregation and is a potent vasoconstrictor.[5] It is rapidly hydrolyzed to thromboxane B_2 at a physiologic pH (half-life of 30 seconds),[5] and the latter, being a more stable prostanoid, has been used for monitoring the production of thromboxane A_2[18, 19] (Fig. 1).

Increased prostacyclin generation in menorrhagia

Primary menorrhagia refers to the menstrual blood loss of more than 80 ml in otherwise healthy women. Although it is a common disorder occurring in some 2% to 10% of the female population, its etiology has remained obscure.[20] Most recent evidence suggests that endometrial prostaglandins may play a role in menorrhagia. This is supported by the data that the uptake of arachidonate into neutral lipids is about twofold higher in menorrhagic endometrium compared to normal endometrium[21] and endometrial levels of prostaglandin E in women with dysfunctional or menorrhagic bleeding are increased.[22-24] The human endometrium and myometrium are also capable of generating prostacyclin and thromboxane A_2,[25, 26] and in view of the potent vascular and platelet actions of prostacyclin and thromboxane A_2 they are more likely candidates for causing menorrhagia than are classical prostaglandins. It is indeed known that the endometrium and myometrium together, but not separately, generate excessive bleeding–promoting prostacyclin in menorrhagia.[24, 27] This implies that the balance between prostacyclin and thromboxane A_2 in the endomyometrium shifts to a dominance of prostacyclin in primary menorrhagia. However, if the endometrial prostaglandin biosynthesis shifts to dominance of the F series, the clinical consequence can be primary dysmenorrhea[3] with normal menstrual blood loss.[28] Nowadays, the most common reason for menorrhagia is the use of an intrauterine contraceptive device, which increases the levels of classical prostaglandins in the endometrium[29] and may also do so in the case of prostacyclin, although no conclusive data exist on this point so far. Further support for the role of increased uterine production of prostacyclin and perhaps prostaglandin E in menorrhagia comes from trials demonstrating that various prostaglandin synthesis inhibitors reduce menstrual blood loss in women with essential and/or intrauterine contraceptive device–induced menorrhagia (Table I). Nevertheless, endometrial fibrinolysis rather than prostanoid release may be a more significant reason for intrauterine contraceptive device–associated menorrhagia, because a fibrinolysis inhibitor (tranexamic acid) is more effective than a prostaglandin synthesis inhibitor (diclofenac sodium) in treatment of intrauterine contraceptive device–induced menorrhagia.[36]

Table I. Reduction by prostaglandin synthesis inhibitors of essential or intrauterine contraceptive device–induced menorrhagia

Treatment	Reason for menorrhagia	No. of patients	*Menstrual blood loss (ml) (mean)*		Reduction (%)	Investigators
			Before treatment	*During treatment*		
Mefenamic acid,* 500 mg 3 times per day during menstruation	Essential	6	119	60	49	Anderson et al.,[30] 1976
Mefenamic acid, 500 mg 3 times per day during menstruation	Intrauterine contraceptive device	15 (menstrual blood loss >80 ml)	104	68	34	Guillebaud et al.,[31] 1978
Mefenamic acid, 500 mg 4 times per day for 3 days	Essential	22 (menstrual blood loss >80 ml)	137	76	45	Haynes et al.,[23] 1980
Naproxen, 500 + 250 + 500 mg for 3 days	Intrauterine contraceptive device	34 (menstrual blood loss >80 ml)	144	108	32	Davies et al.,[32] 1981
1000 mg on day 1 and 750 mg on days 2-3			120	95	22	
Ibuprofen, 400 mg 4 times per day for a maximum of 7 days	Intrauterine contraceptive device	20	72	57	32	Roy and Shaw,[33] 1981
Mefenamic acid, 500 mg 3 times per day during menstruation	Essential	30 (menstrual blood loss >80 ml)	111	77	30	Fraser et al.,[34] 1981
Naproxen, 500 + 250 mg on first 2 menstrual days, 250 mg 2 times per day from day 3 up to 7 days	Essential Intrauterine contraceptive device	4 5	141 172	107 107	24 37	Rybo et al.,[35] 1981
Diclofenac sodium, 50 mg 3 times on day 1 and 25 mg 3 times on menstrual days 2-5	Intrauterine contraceptive device	19 (menstrual blood loss >80 ml)	135	102	20	Ylikorkala and Viinikka,[36] 1983

*One patient received flufenamic acid, 200 mg three times per day.

Prostacyclin and thromboxane in uterine contractility

In view of the uterine production of the smooth muscle–active prostacyclin and thromboxane A_2,[25, 26] one can ask if they have any role in the regulation of uterine contractility.[37] Prostacyclin at concentrations of 100 to 600 ng/ml inhibits the spontaneous activity of strips of nonpregnant human uterus in vitro.[38-40] The half-life of prostacyclin is considerably lengthened in human plasma (up to 60 minutes), presumably because of the binding of prostacyclin to albumin;[41, 42] therefore, the effect of prostacyclin infusion on uterine contractility can also be studied in vivo. Repeated intravenous injections of 2 to 8 μg of prostacyclin had no effect on uterine contractility in four of six nonpregnant women; in the other two there was a slow elevation of uterine tonus.[40] Moreover, intravenous infusion of incremental doses of prostacyclin up to 8 ng/kg/min caused no changes in uterine contractility either during menstruation or in any other phase of the cycle in eight healthy nonpregnant women.[43] With regard to the pregnant uterus, prostacyclin induced a biphasic response with initial stimulation followed by transient inhibition on strips from the upper and lower uterine segments in vitro.[44] In vivo a single dose of 100 μg of prostacyclin given into the extra-amniotic space did not prevent uterine contractions induced with intra-amniotic instillation of a prostaglandin $F_{2\alpha}$ analogue,[39] and intravenous infusion of prostacyclin (up to 8 ng/kg/min) during late pregnancy did not cause labor.[45] Thus prostacyclin has a well-established capacity to change uterine contractility in vitro, but no conclusive evidence exists on its role in uterine contractility in vivo. The vascular smooth muscle seems much more sensitive than myometrium to the action of prostacyclin.

Thromboxane A_2 is also an antagonist of prostacyclin with regard to myometrial contractility, since it contracts the human myometrium in vitro.[40, 46] Thromboxane A_2 does not seem to totally lose this activity during its hydrolysis to thromboxane B_2, because intrauterine instillation of a large dose of thromboxane B_2 (100 μg) clearly elicited uterine contractions in women.[47] This finding may suggest a role of menstrual blood thromboxane B_2 in dysmenorrhea.[46]

Table II. Peritoneal fluid (mean) concentrations of 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2 in patients with endometriosis and control women

	6-Keto-prostaglandin $F_{1\alpha}$ (pg/ml)		*Thromboxane B_2 (pg/ml)*	
Investigators	*Endometriosis*	*No endometriosis*	*Endometriosis*	*No endometriosis*
Drake et al.,[61] 1981	44,500* (n = 14)	3850 (n = 15)	2270† (n = 15)	380
Rock et al.,[58] 1982				
Mild disease	Not measured		88 (n = 15)	132 (n = 17)
Moderate disease			95 (n = 15)	
Severe disease			116 (n = 13)	
Sgarlata et al.,[63] 1983				
Mild disease	920 (n = 8)	1340 (n = 9)	220	420 (n = 9)
Moderate disease	1450 (n = 8)		250	
Severe disease	2370 (n = 9)		550	
Dawood et al.,[59] 1984	3320‡ (n = 16)	480 (n = 10)	114	230
Ylikorkala et al.,[62] 1984				
Mild disease	535 (n = 13)		335	
Moderate disease	792 (n = 8)		612	
Severe disease	1027 (n = 8)		852	
All	742§ (n = 29)	515 (n = 25)	554§	333

*Comparison between endometriosis and no endometriosis groups: $p < 0.01$.
†Comparison between endometriosis and no endometriosis groups: $p < 0.025$.
‡Comparison between endometriosis and no endometriosis groups: $p < 0.02$.
§Comparison between endometriosis and no endometriosis groups: $p < 0.05$.

Effects of estrogens and progestins on prostacyclin and thromboxane

It is well known that women using estrogens are subject to an increased risk of thrombosis, but the causative mechanisms have been poorly understood. Therefore, the effects of estrogens and/or progestins on prostacyclin and thromboxane A_2 have been studied as well. Treatment with combination oral contraceptives increased prostacyclin synthesis in rats[48, 49] and humans[50] when prostacyclin production was assessed by bioassay of prostacyclin-like activity. In contrast, treatment with ethinyl estradiol decreased the release of vascular prostacyclin and increased platelet aggregation in rabbits.[51] In women, the prolonged use of estrogen-containing pills was accompanied by reduced prostacyclin production, as measured by plasma 6-keto-prostaglandin $F_{1\alpha}$, but by no change in plasma or serum thromboxane B_2; the progestogen-only pills had no effect on plasma 6-keto-prostaglandin $F_{1\alpha}$.[52] Furthermore natural estrogens, as used for climacteric replacement therapy, cause no change in plasma 6-keto-prostaglandin $F_{1\alpha}$.[53] These data may imply that synthetic estrogens suppress prostacyclin production perhaps to the extent that such suppression becomes a factor in thrombogenesis during the use of combination oral contraceptives.

Prostacyclin and thromboxane in endometriosis

Mild or moderate endometriosis is often associated with infertility, although the ovaries, tubes, and uterus are apparently healthy. Infertility in these women may be caused by some biochemical abnormality or abnormalities possibly present in the peritoneal fluid bathing the tubes and ovaries. This abnormality may represent the capability of prostacyclin and thromboxane A_2 to change the tuboovarian function.[38, 54-56] Because the volume of peritoneal fluid in patients with endometriosis has been reported to be decreased,[57] normal,[58, 59] or increased,[60] we feel that one should study the concentrations rather than the absolute amounts of prostacyclin and thromboxane A_2 in the peritoneal fluid.

Drake et al.[61] were the first to report increased levels of 6-keto-prostaglandin $F_{1\alpha}$ (a metabolite of prostacyclin) in peritoneal fluid of patients with endometriosis. This finding has been confirmed by two other groups[59, 62] (Table II). Two groups[61, 62] have found increased levels and two other groups[58, 59] normal levels of thromboxane B_2 in peritoneal fluid of patients with endometriosis. Sgarlata et al.[63] found normal levels of 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2 in the peripheral plasma of patients with endometriosis. It is also noteworthy that patients with unexplained infertility[62, 64] had increased peritoneal fluid prostanoids, but those with chronic pelvic inflammatory disease or pain did not.[59] The different antibodies and standards may be one explanation for the marked difference in the absolute levels of peritoneal fluid 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2 (Table II).

It is not definitely known which sources contribute to the peritoneal fluid 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2. They do not originate in the ovaries because they show no cyclic variation and no dependence on the simultaneous levels of ovarian steroids[62] and because the concentrations of 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2 in human follicular fluid are normal in patients with endometriosis and are no higher than those in peritoneal fluid.[65] Perhaps endometriosis implants, which are capable of producing 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2 in vitro,[66] release 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2 into peritoneal fluid. Other possible sources include peritoneal macrophages, retrograde menstruation, and/or the pelvic peritoneum itself.[59, 61, 67] Regardless of the origin of peritoneal fluid 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2, it is tempting to speculate that the possible endometriosis-associated changes in these prostanoids may interfere with ovarian and/or tubal function and thereby contribute to infertility. In view of the alleviation of endometriosis-associated dysmenorrhea by prostaglandin synthesis inhibitors,[68] it is pertinent to ask whether these drugs could be used to improve endometriosis-associated infertility as well.

Prostacyclin and thromboxane in gynecologic cancer

Although it is well established that the conversion of arachidonic acid to classical prostaglandins is increased in cancer cells,[69, 70] there are few studies on the implications of prostacyclin and thromboxane A_2 in cancer. Patients with cervical, endometrial, and ovarian cancer had elevated plasma levels of 6-keto-prostaglandin $F_{1\alpha}$,[71, 72] but these levels became normal after treatment.[72] Also the plasma levels of thromboxane B_2 and the capacity of platelets to produce thromboxane A_2 were increased in patients with ovarian cancer,[73, 74] and the balance between prostacyclin and thromboxane A_2 shifted to a dominance of thromboxane A_2 in patients with gynecologic cancer.[73] This could be one reason for the increased occurrence of thromboembolism in cancer patients. The combined administration of doxorubicin, cyclophosphamide and *cis*-platinum for the treatment of ovarian cancer decreased plasma 6-keto-prostaglandin $F_{1\alpha}$ levels but caused no changes in thromboxane B_2[74]; the infusion of *cis*-platinum alone had no effect on prostacyclin generation.[71] Thus, in addition to the cancer itself, treatment with cytostatic agents may change the prostacyclin/thromboxane A_2 balance.

It is well established that circulating platelets may determine the fate of cancer cells that have entered the circulation.[75] According to this theory, cancer cells that are surrounded by platelets are not destroyed but instead can attach to the vascular endothelium, thereby forming a metastasis. On the other hand, because prostacyclin and thromboxane A_2 potently affect platelet function, a role for these prostanoids in tumor metastasis has been proposed. There is indeed a great deal of evidence from animal experiments that injection of prostacyclin or stimulation of endogenous prostacyclin prevents the formation of metastasis.[75, 76] It seems worthwhile to study whether prostacyclin infusion during cancer operations could prevent metastases in humans, but so far no data exist.

Increased prostacyclin production during pregnancy

The maternal and fetal circulations are characterized by low vascular resistance and vasodilation.[77-79] These changes may be caused by a member of the prostaglandin family,[80] perhaps by prostacyclin. Several pregnancy-associated tissues, such as the human myometrium,[81] decidua, chorion, amnion,[82] and trophoblast,[83] produce the vasodilator prostacyclin in vitro. The production of prostacyclin by the placenta, as seen in many studies,[82, 84-88] has been disputed by one group.[89] Among all pregnancy-associated tissues, the umbilical vessels have the greatest relative prostacyclin production, as shown in various study models with use of the umbilical vessels, microsomes,[90] homogenates,[91-93] rings,[94-98] or whole vessel perfusion.[99] This prostacyclin production may be of utmost importance in the regulation of the umbilical blood flow in humans.[100] The maternal vasculature can also increase its prostacyclin output, as seen from the increased release of prostacyclin by the uterine vessels in pregnant women.[101]

Maternal prostacyclin production in vivo has been measured in terms of plasma 6-keto-prostaglandin $F_{1\alpha}$ by radioimmunoassay[102-106] or with gas chromatography–mass spectrometry.[107] The results are variable, showing decreased,[106] unchanged,[103-105] and increased[107] levels of 6-keto-prostaglandin $F_{1\alpha}$ during pregnancy. In the only longitudinal work, the maternal plasma 6-keto-prostaglandin $F_{1\alpha}$ level increased during the midtrimester, but this rise disappeared in late pregnancy.[102] The maternal plasma 6-keto-prostaglandin $F_{1\alpha}$ is lower than the fetal 6-keto-prostaglandin $F_{1\alpha}$ level, as measured from umbilical cord plasma.[92, 108] Maternal plasma 6-keto-prostaglandin $F_{1\alpha}$ rose during parturition,[108] cesarean section,[109] and vacuum curettage,[110] evidently as a result of the intrauterine prostacyclin release during these events.

The presence of prostacyclin in amniotic fluid has been shown by bioassay of prostacyclin-like activity[111, 112] and by radioimmunoassay of 6-keto-prostaglandin $F_{1\alpha}$.[113-115] The amniotic fluid 6-keto-prostaglandin $F_{1\alpha}$ level increases with advancing gestational age,[112, 115] during labor,[113-116] and with midtrimester abortion.[114] It may originate from various fetoplacental tissues and/or fetal urine.[117]

The measurement of 6-keto-prostaglandin $F_{1\alpha}$ in plasma may not be so reliable an index of prostacyclin production as it was originally thought.[11, 12, 14] Therefore, it was of interest that there were about fivefold increases in the urinary excretion of the enzymatic metabolites of prostacyclin (2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$ and 15-keto-13,14-dihydro-2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$) during pregnancy.[118] This gives further support for the proposal that prostacyclin production increases during pregnancy. It is not known, however, whether this rise comes solely from the maternal vasculature or whether the fetoplacental unit also contributes to it.

Reduced prostacyclin production in preeclampsia

Preeclampsia is characterized by increased blood pressure, general vasoconstriction, and platelet hyperactivity.[78, 119] Theoretically these changes could be caused by a deficient production of the vasodilator and antiaggregator prostacyclin. There is indeed a prostacyclin deficiency in the fetal and maternal tissue, amniotic fluid, and maternal urine in preeclampsia (Table III). However it has remained questionable as to whether this prostacyclin deficiency is a primary change, and thus perhaps a cause of preeclampsia, or whether it reflects some other, more primary changes, such as an increase in lipid peroxides, which is known to occur in preeclamptic women and which can specifically inhibit the synthesis of prostacyclin.[124] Nevertheless preliminary data suggest that a decrease in prostacyclin production precedes the onset of preeclampsia.[125]

Reduced prostacyclin production in nontoxemic complications

Vascular and platelet changes similar to those in preeclampsia can occur in nontoxemic pregnancy complications as well. Maternal smoking causes such changes and may result in spontaneous abortion, prematurity, fetal growth retardation, or fetal death.[126] In theory, these complications could be a result of diminished prostacyclin production, as shown in the umbilical vessels of infants born to smoking mothers in some reports[127, 128] but not all.[99] It is not known which constituent of the cigarette smoke is responsible for the possible reduction in prostacyclin synthesis. It could be nicotine, which inhibits prostacyclin synthesis in cardiovascular tissue[129] and which might have the same effect on human umbilical vessels.[99] Additionally, pregnancy in diabetic women can present complications, possibly as a result of a disturbed vascular-platelet interaction. A prostacyclin deficiency could be a factor, as a deficiency has been detected in the umbilical vessels of infants born to diabetic mothers[97, 130] but not in the amniotic fluid.[116] A prostacyclin deficiency may also be associated with repeated abortions, intrauterine growth retardation, and intrauterine death.[96, 131]

Increased synthesis of thromboxane during pregnancy

All pregnancy-associated tissues (myometrium, decidua, placenta, fetal vessels, and membranes) are known to produce thromboxane A_2 in vitro.[81, 88, 93, 132-135] The order of thromboxane A_2 production by various pregnancy tissue is approximately placenta > decidua > amnion > chorion > myometrium. Thromboxane A_2 production in vivo, as measured by maternal plasma thromboxane B_2 levels, increased during pregnancy in two studies[132, 136] but not in another.[105] A rise in the maternal plasma thromboxane B_2 level could originate from various intrauterine tissues, since operative manipulations were accompanied by rises in maternal plasma thromboxane B_2.[109, 110, 137] The capacity of maternal platelets to synthesize thromboxane A_2 increases during pregnancy.[136] Thromboxane B_2 is also present in amniotic fluid during the midtrimester[114] and at term,[139] and its level increases with advancing gestational age[115] and during labor.[116] In view of the vasoconstricting and proaggregatory action of thromboxane A_2, it has been speculated that it plays a role in placental separation or closure of umbilical vessels after birth.[139]

Increased thromboxane production in preeclampsia

In addition to prostacyclin deficiency, exaggerated thromboxane A_2 generation could, at least in theory, cause platelet-vascular changes pathognomonic for preeclampsia. Maternal plasma thromboxane B_2 levels in pregnancy-induced hypertension were increased in one study[105] but normal in another.[132] The production of malonyldialdehyde by the platelets, which reflects approximately the same pathway as that of thromboxane B_2, is enhanced in pregnancies complicated by chronic placental insufficiency,[140] and the platelet's life span is shortened in preeclampsia as assessed by the recovery of malonyldialdehyde production after aspirin ingestion.[141] Also the placental production of thromboxane B_2 is increased in preeclampsia.[88] Because the balance between prostacyclin and thromboxane A_2, rather than either agent alone, may be a factor in the

Table III. Prostacyclin production in preeclampsia

Investigators	*Biologic sample*	*Preeclamptic patients (n)*	*Control subjects (n)*	*Measurement of prostacyclin*	*Result*
Remuzzi et al.,[120] 1980	Placental/umbilical vessels	5	9	Bioassay in vitro	Reduced
Downing et al.,[90] 1980	Umbilical artery	13	11	Bioassay in vitro	Reduced
Bussolino et al.,[101] 1980	Placental veins, maternal subcutaneous vessels	6	9	Bioassay in vitro	Reduced
Bodzenta et al.,[111] 1980	Amniotic fluid	5	15	Bioassay	Reduced
Ylikorkala et al.,[115] 1981	Amniotic fluid	27	27	Radioimmunoassay of 6-keto-prostaglandin $F_{1\alpha}$	Reduced
Lewis et al.,[121] 1981	Maternal plasma	1	0	Radioimmunoassay of 6-keto-prostaglandin $F_{1\alpha}$	Reduced
Carreras et al.,[95] 1981	Umbilical artery	5	5	Bioassay	Reduced
	Placental vein	5	5	Bioassay	Normal
Stuart et al.,[96] 1981	Umbilical artery	5	32	Conversion of added arachidonic acid to 6-keto-prostaglandin $F_{1\alpha}$	Reduced
Dadak et al.,[97] 1982	Umbilical artery	10	8	Bioassay	Reduced
Mäkilä et al.,[122] 1984	Umbilical artery	9	25	Radioimmunoassay of 6-keto-prostaglandin $F_{1\alpha}$ release during superfusion	Reduced
Ylikorkala et al.,[123] 1981	Maternal plasma	22	22	Radioimmunoassay of 6-keto-prostaglandin $F_{1\alpha}$	Normal
Koullapis et al.,[105] 1982	Maternal plasma	19	141	Radioimmunoassay of 6-keto-prostaglandin $F_{1\alpha}$	Increased
Goodman et al.,[118] 1982	Maternal urine	6	8	Gas chromatographic measurement of 2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$ and 15-keto-13,14-dihydro-2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$	Reduced

regulation of the platelet-vascular function,[9] it is of interest that this balance shifts to a dominance of thromboxane A_2 in amniotic fluid[115] and umbilical vessels[100] in preeclampsia.

Manipulation of prostacyclin and thromboxane in the treatment of hypertensive pregnancies

Although the significance of prostacyclin deficiency and/or thromboxane A_2 overproduction in the development of pregnancy complications is not definitely known and there is no dependence between the human fetoplacental blood flow and maternal plasma 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2,[142, 143] we must still ask whether one can prevent or treat these pregnancy complications by changing prostacyclin and/or thromboxane A_2 levels. Support for this speculation comes from evidence that the infusion of exogenous prostacyclin increases and inhibition of endogenous prostacyclin decreases the uterine blood flow in pregnant animals.[144, 145]

Dietary factors (composition of precursor fatty acids, antioxidants such as selenium and vitamin E, among others), may modify the prostacyclin/thromboxane A_2 balance,[146] but their implications in the synthesis of prostacyclin and thromboxane A_2 during pregnancy have not been thoroughly studied. Nevertheless, preliminary data suggest that increasing the proportion of linoleic acid in the diet may have a small hypotensive effect during pregnancy.[147] In contrast, it is known that synthetic prostacyclin (up to 8 ng/kg/min), when given intravenously to preeclamptic women, drastically reduced maternal blood pressure but caused no changes in uterine contractility or peripheral edema.[45, 148, 149] Platelet consumption was also diminished during prostacyclin infusion.[148] However, improvement in the fetal outcome was unsuccessful in two of three preeclamptic mothers treated with prostacyclin.[149] This may of course stem from the fact that prostacyclin was given too late and only in desperate cases that did not respond to conventional antihypertensive treatment. It is also noteworthy that prostacyclin infusion (up to 8 ng/min/kg) decreased maternal blood pressure in both acute and superimposed preeclampsia without reducing fetoplacental blood flow.[150] Moreover, prostacyclin infusion (5 ng/min/kg) blunted the pressor response to angiotensin II in human pregnancy.[151]

Besides giving exogenous prostacyclin, one may stimulate endogenous prostacyclin. In this regard labetalol hydrochloride, a β- and α-blocking agent, holds considerable promise because it may be an effective treatment of preeclampsia because of its stimulatory effect on prostacyclin and/or inhibitory effect on thromboxane A_2.[148, 152] Also the imidazole derivative dazoxiben hydrochloride can potentiate prostacyclin and inhibit thromboxane B_2 and thereby alleviate preeclampsia.[153] It is further known that magnesium sulfate, which is commonly used for treatment of preeclampsia-eclampsia, stimulates prostacyclin production.[154]

Small doses of aspirin, which would inhibit thromboxane A_2 formation only in the platelets without having any effect on vascular prostacyclin synthesis, are promising in prevention and treatment of cardiovascular disorders.[155-157] The vascular changes in hypertensive pregnancy complications resemble, to some extent, the occlusive vascular disorders in nonpregnant subjects; therefore, one may wonder if aspirin could also prevent vascular disorders during pregnancy. It is already known that the fetal platelet cyclo-oxygenase is 19 times more sensitive to aspirin than umbilical artery cyclo-oxygenase.[158] The inhibition of thromboxane A_2 by aspirin could be one explanation for the preventive[159] and curative effects of aspirin[160] in preeclampsia, as seen in some uncontrolled reports. These provocative theories need to be ascertained in controlled studies, the performance of which is hampered by the knowledge that maternal aspirin or other prostaglandin synthesis inhibitors may cause premature closure of the ductus arteriosus[161] or neonatal bleeding.[162]

In conclusion, during the last decade it has been established that prostacyclin and thromboxane A_2 are important physiologic regulators in reproductive medicine and that disturbances in their balance are related to several gynecologic and obstetric disorders. Still, a final "cause-and-effect relation" between prostacyclin/thromboxane A_2 disturbance and disease-like conditions remains to be proved in future studies. For this purpose it is mandatory to improve the methodology of in vivo prostacyclin and thromboxane A_2 measurements. Future studies may increase the number of gynecologic/obstetric disorders characterized by prostacyclin/thromboxane A_2 abnormalities.

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Hemodynamic observations in severe preeclampsia complicated by pulmonary edema

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Ten patients with severe preeclampsia complicated by pulmonary edema were studied with invasive hemodynamic monitoring. Eight of 10 patients developed pulmonary edema during the postpartum period. Five patients had alterations in the colloid osmotic pressure–pulmonary artery wedge pressure gradient related to elevations in the pulmonary artery wedge pressure and a reduction in the colloid osmotic pressure. Three patients had hemodynamic findings consistent with pulmonary capillary leak. Two patients had evidence of left ventricular failure. In three of the patients, the central venous pressure was significantly lower than the simultaneously determined pulmonary artery wedge pressure during the acute phase of the pulmonary edema. (AM J OBSTET GYNECOL 1985;152:330-4.)

Key words: Severe preeclampsia, pulmonary edema, volume overload, colloid osmotic pressure, pulmonary artery wedge pressure

Pulmonary edema in the pregnant hypertensive patient has been postulated to occur by any one of three mechanisms: increased intravascular hydrostatic pressure, increased capillary permeability, and low vascular oncotic pressure.[1] In nonpregnant patients, the latter mechanism may infrequently cause pulmonary edema but can potentiate its development when combined with either of the first two events.[2] We previously speculated that a reduction in intravascular colloid osmotic pressure may play an important role in the development of pulmonary edema in the hypertensive pregnant patient.[3] However, few patients with pulmonary edema have been subjected to invasive monitoring as well as measurement of colloid osmotic pressure. Since it is difficult to differentiate among the three mechanisms on clinical grounds, little information is available on the frequency with which these various factors lead to the development of pulmonary edema in hypertensive pregnant patients.

Material and methods

This report details the occurrence of pulmonary edema in 10 patients with severe preeclampsia. This series of patients was collected over a 4-year period in two tertiary care referral centers, the University of Washington, Seattle, Washington, and the Inland Empire Perinatal Center, Spokane, Washington. All patients in this series were studied with a flow-directed pulmonary artery catheter either during the development of pulmonary edema or shortly after the development of pulmonary edema but before pharmacologic therapy was directed at relieving the hypoxemia.

Standard clinical procedures were used for care and interpretation of the catheter readings, and standard formulas were used for hemodynamic calculations.[3] The diagnosis of pulmonary edema was made on the basis of the clinical respiratory distress associated with hypoxemia (Po_2 <70 mm Hg with $F_{IO_2} = 0.21$), on blood gas determination, and confirmatory radiographic evidence. Colloid osmotic pressure was either calculated from total protein determination or measured directly by means of a Wescor oncometer.[2]

The diagnosis of left ventricular failure was made when there was increased pulmonary artery wedge pressure associated with a low left ventricular stroke work index.[4, 5] Altered capillary permeability was made when there was a normal pulmonary artery wedge pressure and a normal or elevated left ventricular stroke

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work index (normal left ventricular stroke work index = 55 to 85 gm · min · M^{-2}). Alternatively, this diagnosis was made when the ratio of protein in the pulmonary edema fluid to protein in the patient's serum exceeded 0.4.[6] Altered hydrostatic-oncotic forces were diagnosed when the left ventricular stroke work index was normal and the pulmonary artery wedge pressure was elevated, so that the difference between the colloid osmotic pressure and the pulmonary artery pressure was ≤4 mm Hg (colloid osmotic pressure–pulmonary artery wedge pressure gradient ≤4 mm Hg).

Results

Complete hemodynamic data were available on all 10 patients with acute pulmonary edema. The age range of the patients was from 20 to 37 years (mean, 27 years). Six patients were primiparous, three were secundiparous, and one was grand multiparous. The gestational age range was from 27 to 35 weeks (mean, 31.6 weeks). Nine of the 10 patients were delivered by cesarean section. All patients, except Patient No. 2, were being treated with magnesium sulfate and hydralazine prior to or at the onset of pulmonary edema.

Table I shows the individual hemodynamic data. The patients were categorized on the basis of the mechanism of development of pulmonary edema. Five patients (Nos. 1 through 5) demonstrated alterations in the hydrostatic oncotic forces, three patients (Nos. 6 through 8) showed evidence of permeability pulmonary edema, and two patients (Nos. 9 and 10) showed evidence of left ventricular failure. These data are graphically plotted in Fig. 1.

Table II illustrates the time of onset of pulmonary edema and the relationship to measured filling pressures. For eight of the 10 patients, pulmonary edema developed after delivery. The range of onset was 5 to 24 hours (mean, 12.6 hours). Six of the eight patients developed respiratory insufficiency between 9 and 15 hours post partum. In all patients, central venous pressure immediately post partum was between 0 and 6 mm Hg. However, there was a progressive rise in the central venous pressure in most of the patients until the onset of pulmonary edema was recognized. In three of the patients (Nos. 1, 3, and 8), the measurements of central venous pressure did not reflect the simultaneously recorded wedge pressure. In those three patients, the wedge pressure was significantly higher than the central venous pressure.

Table III illustrates the volume status of each patient in the critical period before the onset of pulmonary edema. Large volumes of fluid were frequently justified by clinical need (preoperative hypotension, preload for anesthesia). In some cases, the large volumes of fluid were the result of intraoperative administration of blood and crystalloid to correct intraoperative loss, intraoperative falls in blood pressure, coagulopathy, or thrombocytopenia.

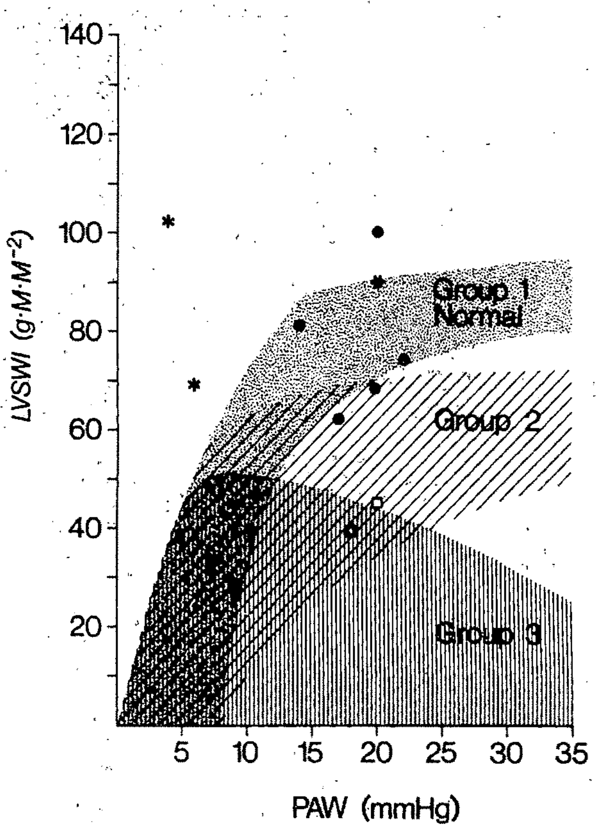

Fig. 1. Ventricular function curve[5] illustrating myocardial performance for each of 10 patients listed in Table I. *LVSWI*, Left ventricular stroke work index. *PAW*, Pulmonary artery wedge pressure. ● Patients 1 through 5. *Patients 6 though 8. □ Patients 9 and 10.

Comment

In this group of patients, the most common reasons for the development of pulmonary edema was an alteration in the hydrostatic oncotic forces that occurred within 15 hours post partum. This alteration in forces occurred because of a combination of mild-to-moderate lowering of colloid osmotic pressure (mean = 15.3 mm Hg) and mild-to-moderate elevations in the left ventricular filling pressures reflected by the pulmonary artery wedge pressure (mean, 18.6 mm Hg). None of these patients had evidence of left ventricular dysfunction, and the elevations in filling pressures were not of significant magnitude to account for pulmonary edema without simultaneous lowering of intravascular oncotic forces.

All patients except Nos. 4 and 8 received colloidal fluid prior to the onset of the pulmonary edema. This

Table I. Hemodynamic data

Patient No.	*Blood pressure*	*Cardiac output (L/min)*	*Cardiac index (L/min/m²)*	*Stroke volume (ml)*	*Pulmonary artery systolic pressure (mm Hg)*	*Pulmonary artery diastolic pressure (mm Hg)*	*Pulmonary artery wedge pressure (mm Hg)*	*Central venous pressure (mm Hg)*
1	155/105	7.6	4.25	80	35	25	22	7
2	160/110	12.5	7.2	101	34	16	20	15
3	130/100	8.9	4.9	89	30	18	17	10
4	182/116	7.9	4.9	78	22	15	14	14
5	140/60	8.5	5.0	85	40	20	20	16
6	160/90	13.3	6.9	133	23	8	4	8
7	171/98	8.1	4.4	81	22	10	6	6
8	160/80	11.0	6.9	103	35	20	20	10
9	164/82	6.6	3.4	75	40	20	20	18
10	130/90	4.3	2.7	54	34	20	18	12

Patients 1 through 5: Altered hydrostatic forces. Patients 6 through 8: Permeability defect. Patients 9 and 10: Left ventricular failure.

Table II. Filling pressures and time of onset of pulmonary edema

*Patient No.**	*Onset of pulmonary edema (hr)*	*Postpartum central venous pressure (0-1 hr) (mm Hg)*	*Central venous pressure at onset of pulmonary edema (mm Hg)*	*Pulmonary artery wedge pressure at onset of pulmonary edema (mm Hg)*
1	12 Hr postpartum	6	7	22
2	Antepartum	NA	15	20
3	12 Hr post partum	6	10	17
4	12 Hr post partum	5	14	14
5	9 Hr post partum	0	16	20
6	24 Hr post partum	0	8	4
7	12 Hr post partum	3	6	6
8	5 Hr post partum	5	10	20
9	Antepartum	NA	18	20
10	15 Hr postpartum	6	12	18

NA = Not available.

*Patients as in Table I. See footnote.

Table III. Fluid management

Patient No.	*Fluid preceding pulmonary edema*	*Rationale for fluid*	*Fluid components*	*Anesthesia/delivery*	*Other factors*
1	5000 ml/24 hr	Intraoperative replacement	Crystalloid + colloid + blood	General anesthesia, cesarean section	Quadruplets
2	9000 ml/24 hr	Hypotensive after epidural anesthesia	Crystalloid + colloid	Epidural anesthesia, cesarean section	
3	1000 ml/5 hr	Low hematocrit (28)	Blood	General anesthesia, cesarean section	
4	6500 ml/12 hr	Oliguria	Crystalloid	General anesthesia, cesarean section	
5	7000 ml/12 hr	Preload for epidural anesthesia	Crystalloid + colloid	Epidural anesthesia, cesarean section	
6	4500 ml/24 hr	Excess intravenous intake	Crystalloid + colloid	General anesthesia, cesarean section	
7	7000 ml/3 hr	Hypotension	Crystalloid + colloid + blood	General anesthesia, cesarean section	Eclampsia, hepatic rupture
8	6000 ml/24 hr	Intraoperative replacement	Crystalloid	General anesthesia, cesarean section	Twins
9	5500 ml/24 hr	Excess intravenous and oral intake	Crystalloid + colloid	Epidural anesthesia, cesarean section	Diabetes, chronic hypertension
10	7000 ml/12 hr	Intraoperative replacement	Crystalloid + colloid + blood	General anesthesia, cesarean section	Thrombocytopenia

Colloid osmotic pressure (mm Hg)	*Systemic vascular resistance (dynes-sec · cm⁻⁵)*	*Left ventricular stroke work index (gm · min · M⁻²)*	*Colloid osmotic pressure—pulmonary artery wedge pressure gradient (mm Hg)*
10.4	1206	74	−11.6
18.8	714	100	−1.2
15.6	885	62	−1.4
14.8	1357	82	0.8
17.9	978	68	−2.0
17.2	631	102	13.0
16.5	1145	69	10.5
11.9	557	90	−8.0
17.9	823	46.4	−2.0
16.5	1693	39	−1.5

fluid (blood products and albumin) is known to have strong osmotic effects on the movement of fluid between the intravascular and extravascular space. When fluid is administered to the severely preeclamptic patient, movement of significant amounts of fluid from the overexpanded extravascular space to the intravascular space can result. We hypothesize that, when this effect is added to the usual mobilization of fluid from extravascular compartment to intravascular compartment that occurs after delivery, a progressive rise in the pulmonary artery wedge pressure occurs. Our data are consistent with this hypothesis.

It was previously shown that pregnancy results in the lowering of the colloid osmotic pressure, and that the preeclamptic patient has colloid osmotic pressure even lower than that of the normal pregnant patient.[3] The colloid osmotic pressure falls in the postpartum period both in normal and in preeclamptic pregnancies. The combination of a low intravascular oncotic pressure and a progressive rise in hydrostatic pressure can explain pulmonary edema in these patients. The most frequent time for this to occur was within 15 hours post partum (Table II). In light of these observations, we think that it is wise to monitor central pressures closely in the postpartum period in severely preeclamptic patients who have received significant amount of colloidal fluid in the antepartum or intraoperative period.

Many authors have questioned the administration of colloidal fluid to the severely hypertensive patient. We previously advised giving only maintenance fluid during labor.[3] However, clinical circumstances may dictate the need for a colloidal fluid. These circumstances include acute volume loss, severe thrombocytopenia, or coagulopathy. We also have used volume loading with a combination of crystalloid fluid and colloidal fluid prior to the induction of epidural anesthesia, and have shown that when this is expertly done, with adequate monitoring of vascular pressure, it is safe for both the fetus and the mother.[7] The use of colloidal fluid without adequate monitoring of pressure may increase the risk of pulmonary edema.

The second most common mechanism for the development of pulmonary edema was alteration in capillary permeability. One of these three patients (No. 8) was the only fatality in the series. She developed acute respiratory insufficiency within 12 hours post partum and initially showed elevated filling pressures. However, after diuresis had lowered the pulmonary artery wedge pressure to 12 mm Hg, she began to exude large amounts of proteinaceous material from the endotracheal tube. She eventually developed chronic adult respiratory distress syndrome and died on the twenty-second post partum day. Sectioning of the lungs at autopsy provided no evidence for amniotic fluid embolism. The other two patients showed normal ventricular function and normal wedge pressures in the face of altered oxygenation, and both recovered. Altered capillary permeability can develop in other organ systems, such as the kidney. In severe preeclampsia, permeability defects in the lungs are uncommon, and the triggering mechanism is frequently associated with acute volume loss or amniotic fluid embolism, or sepsis.[8]

Two patients showed evidence of ventricular failure. Patient No. 9 had multiple medical problems, so that ventricular failure in this patient was not surprising. However, the other patient had no predisposing factors and her left ventricular dysfunction was rather transient, lasting only 8 hours. Potent diuresis led to a lowering of the pulmonary artery wedge pressure to 12 mm Hg, which resulted in the normalization of cardiac performance. Other investigators[7] have reported left ventricular failure as a result of high systemic resistance which responded to afterload reduction.

Most patients in this series had received large amounts of fluid prior to the development of pulmonary edema. This was often not appreciated by the physicians until pulmonary edema developed post partum. One reason for the excess volume given during the intraoperative period in some patients was a precipitate fall in blood pressure just after the delivery of the fetus. Fig. 2 illustrates simultaneous recordings of the pulmonary artery pressure and the intra-arterial pressure in a patient who experienced a fall in blood pressure. In our experience, this event has usually not been associated with excessive volume loss. The precipitate fall in intravascular pressures occurs in both the systemic and pulmonary circulations. This phenomenon might be explained by the relief of a selective aortic obstruction by the gravid uterus. In that case, the pregnant uterus might have been acting in a fashion similar to an antigravity suit. The delivery of the fetus would relieve the obstruction and create a large, transiently underfilled space. This would result in a precipitate fall in pressure until adequate volume homeostasis was restored.

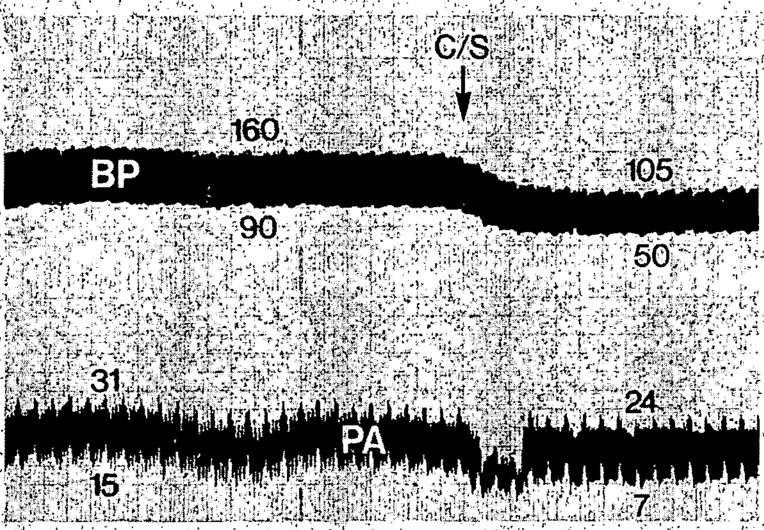

Fig. 2. Intra-arterial *(BP)* and pulmonary *(PA)* pressure during cesarean section *(C/S)* delivery. Paper speed is 3 cm/min.

The usual treatment of this event is with intravenous ephedrine and volume replacement. If this volume replacement is administered by the anesthesiologist without good communication with the obstetrician, serious volume overload in the postpartum period can result as the fluid is mobilized from the overloaded extravascular space. Further investigation into this event is necessary to determine etiologic mechanisms and whether pharmacologic intervention without volume replacement will correct this hypotensive event.

This study again demonstrated the poor correlation between the central venous pressure and the pulmonary artery wedge pressure in some patients with severe preeclampsia. This observation has been made in patients without pulmonary edema as well as in those with pulmonary edema.[9, 10] In this series, five of 10 patients had a difference of ≥5 mm Hg, and two patients had a difference of ≥10 mm Hg. This difference appears to become clinically relevant when the central venous pressure exceeds 6 mm Hg. Neither this study nor any other in the literature shows any patients in whom the central venous pressure was 6 cm or less accompanied by an elevation in pulmonary artery wedge pressure that could potentiate the development of pulmonary edema. It is important to recognize that patients in whom the central venous pressure is consistently greater than 6 mm Hg may have a much higher pulmonary artery wedge pressure. If respiratory insufficiency develops, a pulmonary artery catheter should be used to characterize the hemodynamic picture so that appropriate therapy can be selected and the response to therapy monitored.

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Preeclampsia: An imbalance in placental prostacyclin and thromboxane production

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Preeclampsia is characterized by increased vasoconstriction frequently associated with increased platelet aggregation, reduced uteroplacental blood flow, and premature delivery. Because prostacyclin antagonizes the vasoconstrictor, platelet-aggregating, and uterine-activating actions of thromboxane, we considered the hypothesis that placental production of thromboxane was increased coincident with decreased production of prostacyclin in preeclampsia. Fresh human term placentas were obtained immediately after delivery from 11 normal and 10 preeclamptic pregnancies (blood pressure $\geq$140/90 mm Hg, urinary protein >0.3 gm/24 hr). Tissues (350 mg) were incubated sterilely in 6 ml of Dulbecco's Modified Eagle's Medium for 48 hours at 37° C with 95% oxygen and 5% carbon dioxide in a metabolic shaker. Samples were collected at 8, 20, 32, and 48 hours and analyzed for thromboxane by radiommunoassay of its stable metabolite, thromboxane B_2, and for prostacyclin by radioimmunoassay of its stable metabolite, 6-keto prostaglandin $F_{1\alpha}$. The production of thromboxane was significantly increased in preeclamptic versus normal placental tissue (22.9 ± 4.7 versus 6.3 ± 1.5 pg/mg/hr, mean ± SE, $p < 0.01$), whereas the production of prostacyclin was significantly decreased (3.0 ± 0.3 versus 6.7 ± 0.5 pg/mg/hr, $p < 0.001$). In both normal and preeclamptic placentas, the production rates of thromboxane and prostacyclin were inhibited by indomethacin (5 μmol/L) and not affected ($p > 0.50$) by arachidonic acid (100 μmol/L). Therefore, during normal pregnancy, the placenta produces equivalent amounts of thromboxane and prostacyclin, so that their biologic actions on vascular tone, platelet aggregation, and uterine activity will be balanced. In preeclamptic pregnancy, however, the placenta produces seven times more thromboxane than prostacyclin. (AM J OBSTET GYNECOL 1985;152:335-40.)

Key words: Preeclampsia, placenta, prostacyclin, thromboxane, pregnancy

We previously reported that the placental production of prostacyclin is significantly decreased in preeclamptic pregnancies as compared to normal pregnancies.[1] Since prostacyclin is a potent vasodilator and an inhibitor of platelet aggregation,[2] a deficiency in the production of it during pregnancy could contribute to the clinical manifestations of preeclampsia. On the other hand, since thromboxane is a potent vasoconstrictor and a stimulator of platelet aggregation,[2] it opposes the actions of prostacyclin. It occurred to us that the deficiency in prostacyclin production by preeclamptic placentas could be coupled to an enhanced production of thromboxane. This situation could profoundly and adversely affect uteroplacental blood flow, growth of the fetus, and maternal vascular changes.

The production of thromboxane is increased during normal pregnancy because maternal plasma levels are higher during late pregnancy than during midpregnancy and in the nonpregnant state.[3] The source of the additional circulating thromboxane could be the placenta, because it produces thromboxane.[4] Since placental production of thromboxane has not been reported in preeclampsia, we undertook to determine the simultaneous production rates of thromboxane and prostacyclin by normal and preeclamptic placentas.

Material and methods

Term placentas were obtained within 15 minutes of delivery from 11 healthy, normotensive women and from 10 women with a clinical diagnosis of preeclampsia. A mixture of vaginal and cesarean section deliveries was included in each group. The following criteria were used for the normal pregnancies: maternal blood pressure (systolic/diastolic) $\leq$110/70 mm Hg; no protein-

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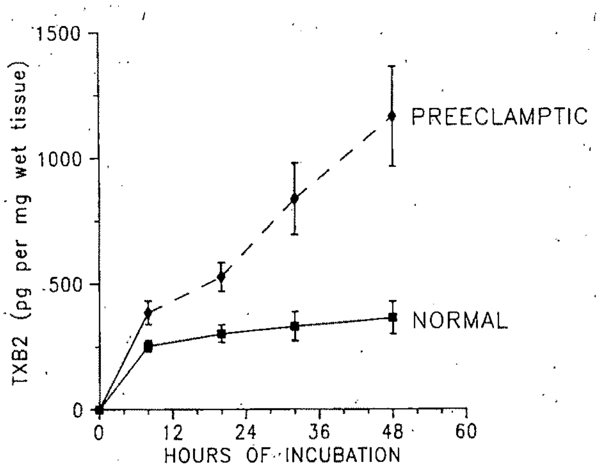

Fig. 1. Production rates of thromboxane by normal and preeclamptic placental tissues, as estimated by the concentrations of its stable metabolite, thromboxane B_2 *(TXB2)* in the incubation medium. Preeclamptic versus normal production rate = 22.9 ± 4.7 versus 6.3 ± 1.5 pg/mg of wet tissue per hour, $p < 0.01$, or 335 versus 92 μg/day. Data represent mean ± SE (n = 10 versus 11).

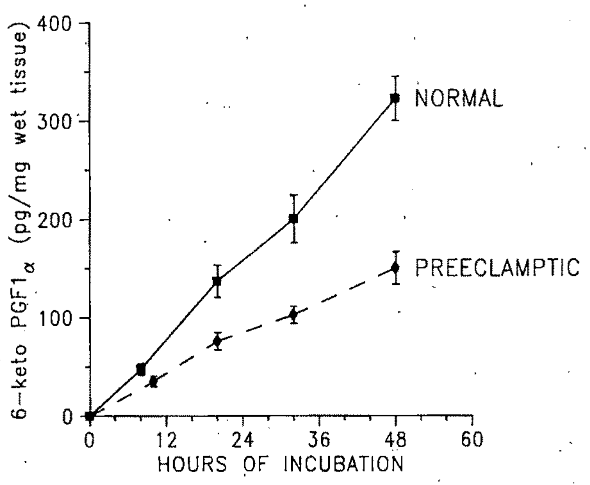

Fig. 2. Production rates of prostacyclin by normal and preeclamptic placental tissues, as estimated by the concentrations of its stable metabolite, 6-keto prostaglandin $F_{1\alpha}$ *(6-keto PGF1α)*, in the incubation medium. Preeclamptic versus normal production rate = 3.0 ± 0.3 versus 6.7 ± 0.5 pg/mg of wet tissue per hour, $p < 0.001$, or 44 versus 97 μg/day. Data represent mean ± SE (n = 10 versus 11).

uria; gestational length between 36 and 43 weeks; duration of labor less than 18 hours for primigravid patients and less than 12 hours for multigravid patients; no overt medical complications, such as diabetes, chronic infection, or metabolic, endocrine, nutritional, or hematologic complications; no neonatal abnormalities, such as developmental defects, abnormal Apgar scores (1- and 5-minute tests), or birth weights less than 2.5 kg or greater than 4.5 kg; no third-trimester bleeding; no gross placental abnormalities; no positive findings in high-risk antenatal assessment; no oligohydramnios or polyhydramnios; no or minimal alcohol consumption or smoking during pregnancy. The same criteria were used to assess the preeclamptic pregnancies, except: maternal blood pressure (systolic/diastolic) ≥140/90 mm Hg on two separate readings 6 hours apart; proteinuria, urinary protein >0.3 gm/24-hour urine collection.

Placental tissues were immediately chilled and processed under strict sterile conditions at 4° C. Placental tissues were separated, gently cut into small pieces, and washed repeatedly with buffer. Excess buffer was removed with sterile gauze. Each tissue (350 mg) was incubated in duplicate in 6 ml of Dulbecco's Modified Eagles Medium (Dulbecco's MEM) (Gibco, Grand Island, New York) for 48 hours at 37° C in a Dubnoff metabolic shaker. Tissues were oxygenated with 95% oxygen and 5% carbon dioxide. Partial pressures and hydrogen ion concentrations in the incubation medium were consistent at approximately $Po_2 = 250$ mm Hg, $Pco_2 = 20$ mm Hg, and pH = 7.50. Indomethacin and arachidonic acid were obtained from Sigma Chemical Co., St. Louis, Missouri.

Samples (200 μl) were collected at 0 hours and at 8, 20, 32, and 48 hours of incubation. The production of thromboxane A_2 was estimated by determining the concentration in the incubation medium of one of its stable metabolites, thromboxane B_2. A highly specific radioimmunoassay was used. Briefly, the assay consisted of competitive binding of radioactive and natural thromboxane B_2 to a highly specific antibody. Dextran-coated charcoal was used to separate the bound from the free fraction. The antibody was obtained from Seragen, Inc., Boston, Massachusetts, and radioactive thromboxane B_2 from New England Nuclear, Boston, Massachusetts. Cross-reactivity of the antibody with other possible interfering eicosanoids was less than 0.1% for $PGF_{1\alpha}$, 6-keto-$PGF_{1\alpha}$, $PGF_{2\alpha}$, PGE_1, PGE_2, PGD_2, PGA_1, PGA_2, PGB_1, PGB_2, 5-HETE, 12-HETE, 15-HETE, 13,14-dihydro-15-keto-PGE_1, and 13,14-dihydro-15-keto-$PGF_{1\alpha}$. The following radioimmunoassay validations are for the assays in which the patients reported on in this study were run. Within-assay and between-assay variations were each tested at three different positions of the standard curve in five different assays. Within-assay variation was ≤9.3%, and between-assay variation was ≤7.8% (n = 5). The least detectable concentration was 4.4 ± 1.4 pg, and 50% binding of the standard curve was 46 ± 9 pg (mean ± SE, n = 5). Serial sample dilutions were parallel to the standard curve (slope comparisons: $p > 0.50$), and the addition of increasing amounts of thromboxane B_2 to Dulbecco's

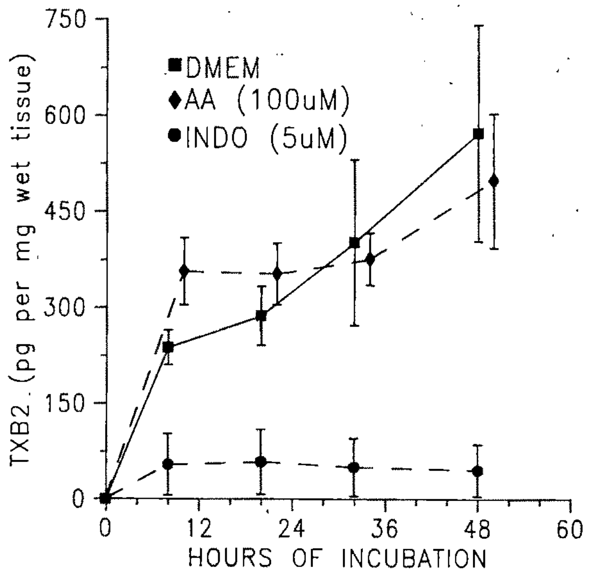

Fig. 3. Effects of indomethacin *(INDO)* (5 μmol/L) (n = 3) and arachidonic acid *(AA)* (100 μmol/L) (n = 7) on thromboxane *(TXB2)* production by normal placental tissue. Thromboxane production was significantly ($p < 0.001$) inhibited by indomethacin but not affected ($p > 0.10$) by arachidonic acid. Data represent mean ± SE. *DMEM,* Dulbecco's Modified Eagle's Medium.

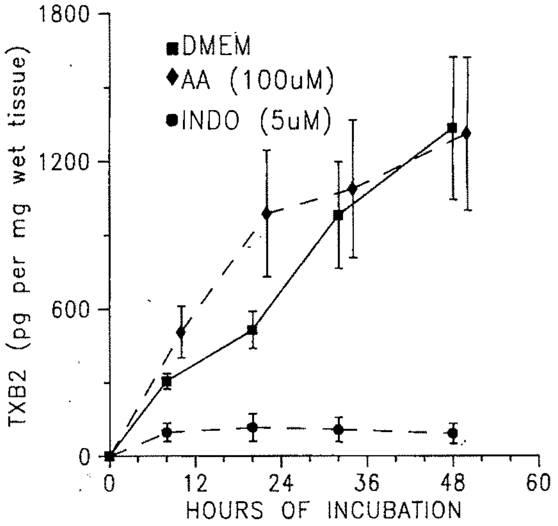

Fig. 4. Effects of indomethacin *(INDO)* (5 μmol/L) (n = 3) and arachidonic acid *(AA)* (100 μmol/L) (n = 6) on thromboxane production by preeclamptic placental tissue. Thromboxane production was significantly ($p < 0.001$) inhibited by indomethacin but not affected ($p > 0.10$) by arachidonic acid. Data represent mean ± SE. *DMEM,* Dulbecco's Modified Eagle's Medium.

MEM resulted in a linear dose response ($r^2 = 0.971$, $y = 0.83 + 1.13x$, n = 5). Dulbecco's MEM alone resulted in a zero dose response.

The production of prostacyclin was determined by a specific radioimmunoassay of its stable metabolite, 6-keto prostaglandin $F_{1\alpha}$ (6-keto $PGF_{1\alpha}$). The radioimmunoassay procedure was similar to that described above for thromboxane B_2. Its validation was published previously.[1] The thromboxane and prostacyclin radioimmunoassays were validated according to the methods of Rodbard.[5]

Tissue viability after 48 hours of incubation was assessed by trypan blue exclusion staining of trypsinized dispersed cells, as described previously.[1] Production rates were determined by calculating the slopes of the regression lines. Statistical differences between production rates were assessed by the *t* test, and differences between regression lines by analysis of variance (between-within, two-factor mixed design[6]). Data were expressed as picograms per milligram of wet tissue.

Results

There were no significant differences ($p > 0.50$) between normal and preeclamptic pregnancies for placental weights (606 ± 92 versus 610 ± 66 gm, respectively, mean ± SD), fetal weights (3.45 ± 0.45 versus 3.54 ± 0.23 kg), weeks of gestation at delivery (39 ± 1 versus 38 ± 1), and 1-minute Apgar scores of the fetuses (8.0 ± 0.9 versus 7.9 ± 0.6). All fetuses were healthy. The preeclamptic mothers were slightly younger than the normal mothers (23.2 ± 3.8 versus 30.1 ± 3.7 years) and gained more weight during their pregnancies (42.8 ± 13.5 versus 30.7 ± 8.4 pounds). Tissue viability as assessed by trypan blue exclusion staining was greater than 95% after 48 hours of incubation in both normal and preeclamptic placentas. There were five vaginal and six cesarean section deliveries in the normal group, and eight vaginal and two cesarean section deliveries in the preeclamptic group. The time in labor was 9.5 ± 4.0 versus 10.4 ± 4.4 hours (normal versus preeclamptic, $p > 0.50$). Time in labor was not correlated with the production of thromboxane or prostacyclin ($r = -0.10$ and 0.05, respectively). Three of the normal patients and all of the preeclamptic patients were primigravid. One of the preeclamptic patients had severe preeclampsia (systolic/diastolic blood pressure ≥170/110 mm Hg).

The production of thromboxane by normal placental tissue, as estimated by thromboxane B_2, is shown in Fig. 1. The concentrations of thromboxane B_2 in the incubation medium increased progressively during the 48 hours of incubation. Peak levels after 48 hours averaged 363 pg/mg. The production rate was 6.3 ± 1.5 pg/mg/hr (mean ± SE, n = 11).

In comparison to normal tissue, the production of thromboxane by preeclamptic placentas was considerably elevated (Fig. 1). The concentrations of thromboxane B_2 in the incubation medium were significantly

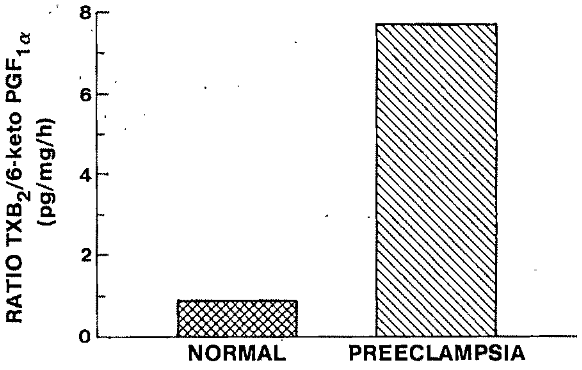

Fig. 5. Ratios of the placental production rates of thromboxane to prostacyclin *(TXB$_2$/6-keto PGF$_{1\alpha}$)* in normal and preeclamptic pregnancies.

greater than those for normal placentas ($p < 0.001$). Peak levels at 48 hours averaged 1164 pg/mg compared to 363 pg/mg for normal placentas. The production rate for the preeclamptic placentas was 22.9 ± 4.7 pg/mg/hr (mean ± SE, N = 10), and this was significantly greater than the production rate for the normal placentas of 6.3 pg/mg/hr ($p < 0.001$).

The production rates of prostacyclin for normal and preeclamptic placental tissues, as estimated by 6-keto PGF$_{1\alpha}$, are shown in Fig. 2. As was true for thromboxane, the concentrations of 6-keto PGF$_{1\alpha}$ in the incubation medium increased progressively and in a linear fashion during the 48 hours of incubation. Peak levels after 48 hours averaged 322 pg/mg for normal tissue and 151 pg/mg for preeclamptic tissue. The production rate was 6.7 ± 0.5 pg/mg/hr (mean ± SE, n = 11) compared to 3.0 ± 0.3 pg/mg/hr (n = 10) for normal and preeclamptic placentas, respectively. The production rate of prostacyclin was significantly lower ($p < 0.001$) in preeclamptic than in normal placentas. These prostacyclin data are not significantly different ($p > 0.5$) from our previously published data.[1]

To assure that we were measuring thromboxane production rather than tissue release, and to assure that our production rates were not limited because of precursor availability, some tissues were incubated in Dulbecco's MEM with varying concentrations of either indomethacin or arachidonic acid. The production of thromboxane was completely inhibited by 50 μmol/L of indomethacin; whereas 5 μmol/L of indomethacin allowed a slight amount to be produced in normal tissue (0.61 ± 0.57 pg/mg/hr, n = 3, Fig. 3) and preeclamptic tissue (1.58 ± 0.69 pg/mg/hr, n = 3, Fig. 4). The addition of arachidonic acid (100 μmol/L) did not significantly affect ($p > 0.10$) the production of thromboxane in either normal or preeclamptic placentas (Figs. 3 and 4). The production rates in normal placentas with and without arachidonic acid were 8.0 ± 1.8 versus 10.7 ± 3.8 pg/mg/hr (n = 7), and in preeclamptic placentas they were 25.7 ± 6.7 versus 27.7 ± 6.9 pg/mg/hr (n = 6), respectively.

We previously reported that placental production of prostacyclin is inhibited by indomethacin and not affected by the addition of arachidonic acid.[1] These statements are also true for the present study.

Comment

The production of thromboxane by preeclamptic placentas was significantly greater than that by normal placentas (Fig. 1). The preeclamptic placenta produced over three times as much thromboxane as the normal placenta. This sharply contrasted with the production rates of prostacyclin. The preeclamptic placenta produced less than one half as much prostacyclin as the normal placenta[1] (Fig. 2). Perhaps even more interesting are the ratios of thromboxane to prostacyclin in normal versus preeclamptic pregnancies. In normal pregnancy, the placenta produced approximately equal amounts of prostacyclin and thromboxane, but the preeclamptic placenta produced over seven times as much thromboxane as prostacyclin (Fig. 5).

Because of the biologic actions of these eicosanoids, this imbalance could significantly contribute to the increased vasoconstriction, platelet aggregation, and reduced uteroplacental blood flow characteristic of preeclampsia.[7-9] In regard to premature labor, exact statistics are difficult to obtain because most premature preeclamptic deliveries are induced by the physician because of maternal complications. Nonetheless, preeclampsia is considered to be one of the causes of preterm labor.[10] The increased thromboxane and decreased prostacyclin imbalance of the preeclamptic placenta might contribute to premature labor because prostacyclin inhibits[11, 12] and thromboxane stimulates uterine activity.[11]

The fact that prostacyclin and thromboxane can affect the human placental vasculature was recently demonstrated with an in vitro placental perfusion system.[13] When compounds were infused into the fetal side of the placenta, a thromboxane mimic increased placental vascular resistance, whereas prostacyclin attenuated the vasoconstrictor effects of angiotensin II. When compounds were infused from the maternal side, no placental vascular effects were observed, thus indicating that prostaglandins and thromboxanes do not readily cross the placenta.

In the maternal cotyledonary placenta of the sheep, prostacyclin did not attenuate the vasoconstrictor effects of angiotensin II in vivo.[14] The sheep maternal placenta, however, may not be a good model for the primate placenta because of physiologic and/or anatomic differences. The sheep has an epitheliochorial, cotyledonary type of placenta with a distinct maternal placenta. The primate has a hemochorial, discoidal type of placenta with no distinct maternal placenta. Teleologically, one might consider the maternal cotyledonary placenta of the sheep to be homologous to the decidua of the primate, and the sheep fetal cotyledonary placenta to be homologous to the primate discoidal placenta. If one accepts this reasoning, then the fetal rather than the maternal placenta in sheep might be the better model for the primate placenta. Infusions of prostacyclin and thromboxane have not as yet been done in fetal sheep to test the vasoactive effects of them on the fetal placenta.

The increased vascular congestion and platelet aggregation of preeclamptic placentas[7, 8, 15, 16] might also be explained by the local placental imbalance of increased thromboxane and decreased prostacyclin. Because the placenta produces these eicosanoids, one would expect the concentrations of them in the placental vasculature to be considerably higher than in the maternal peripheral circulation, which would lead to an intensification of their effects in the placental blood vessels. In preeclampsia, the effects of thromboxane to increase vasoconstriction and platelet aggregation would predominate.

In vivo, it is probable that the increased platelet aggregation leads to a further increase in the concentrations of thromboxane locally in the preeclamptic placental vasculature, because platelets produce thromboxane during the aggregation process. Increased platelet numbers, however, cannot account for our in vitro results for the following reasons. (1) The placental tissues were thoroughly blanched before incubation by first perfusing the placental vasculature with buffer to remove fetal blood, then by placing a small piece of tissue in buffer and vigorously agitating it by bubbling 95% oxygen and 5% carbon dioxide to remove maternal blood. (2) Histologic examination of trypsinized dispersed cells demonstrated that few blood cells of any kind were present in our incubated tissues. (3) Aggregated platelets adhering to vascular walls would have released their thromboxane during the aggregation process. (4) The small number of platelets present in the in vitro incubates could not possibly account for the tremendous rate of production of thromboxane by the preeclamptic placenta. The production rate is expressed as picograms per milligram of wet placental tissue per hour. Even if the placental tissues were filled with blood, the platelets could only account for 1% of the total blood volume and, certainly, an even smaller percentage of the combined total placental wet tissue weight.

We have considered that placentally produced prostacyclin and thromboxane are primarily important in the local regulation of uteroplacental blood flow. However, systemic effects in the mother and fetus of these placentally produced eicosanoids cannot be ruled out. They are apparently secreted into the maternal and fetal circulations because the concentrations of them are considerably higher in the uterine and umbilical veins than in the maternal peripheral circulation.[17] In patients with preeclampsia, an imbalance of increased thromboxane and decreased prostacyclin existed in the vessels draining the placenta, an imbalance that persisted in the maternal circulation.[17]

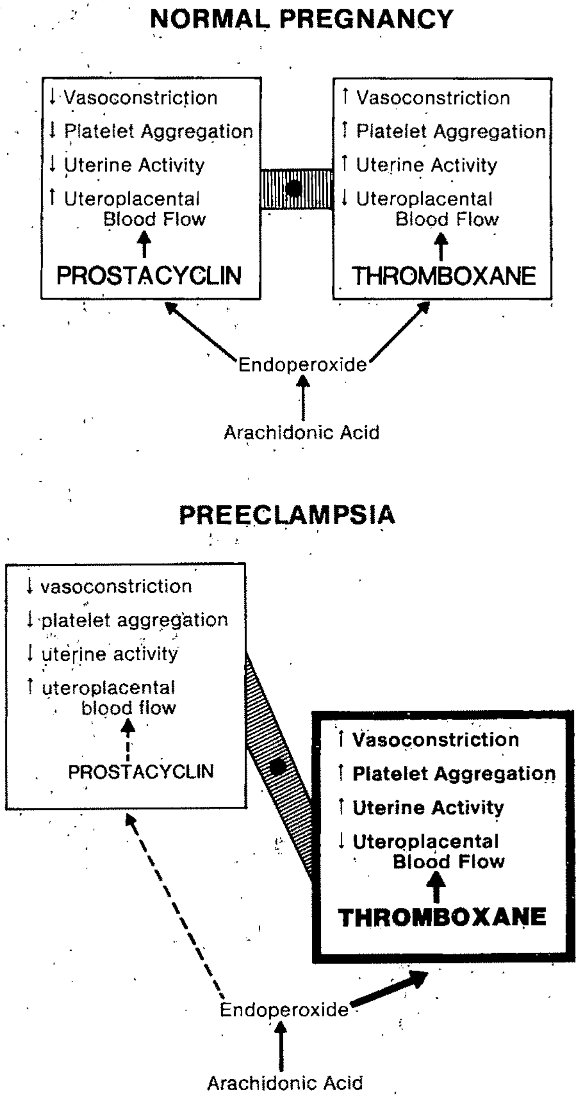

Fig. 6. Comparison of the balance in the biologic actions of prostacyclin and thromboxane in normal pregnancy with the imbalance of increased thromboxane and decreased prostacyclin in preeclamptic pregnancy. The heavy type and box for thromboxane suggest an exacerbation of its actions in preeclampsia, whereas the lighter type and box for prostacyclin suggest a diminution of its actions.

The thromboxane/prostacyclin imbalance could reduce the blood flow from the placenta to the fetus because thromboxane constricts and prostacyclin dilates the umbilical artery.[18] Additionally, the distribution of blood flow within the fetus might be altered because the increased ratio of thromboxane to prostacyclin might cause vasoconstriction of the ductus arteriosus and pulmonary vasculature.[19-21]

Robinson et al.[22] measured the tissue levels of thromboxane in normal and preeclamptic placentas and found no difference. We also found no difference in the concentrations of thromboxane in medium between normal and preeclamptic placentas in samples collected at zero hour. Because eicosanoids, like steroids, are not stored by tissues, we believe that the production rate, which demonstrates the propensity of a tissue to produce a substance, is a better indicator of the in vivo situation than simply the tissue level.

In conclusion, during normal pregnancy, the placenta produces equivalent amounts of prostacyclin and thromboxane, so that the biologic actions of them on vascular tone, platelet aggregation, and uterine activity will be balanced (Fig. 6). However, in preeclamptic pregnancy, placental production of these two eicosanoids is tipped heavily in favor of thromboxane. Therefore, the actions of thromboxane to increase vasoconstriction, platelet aggregation, and uterine activity will be exacerbated, whereas the actions of prostacyclin to promote vasodilatation and inhibit platelet aggregation and uterine activity will be diminished.

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The relationship of fetal plasma protein concentration and hemoglobin level to the development of hydrops in rhesus isoimmunization

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Fetoscopic samples of pure fetal blood were obtained at 18 to 25 weeks' gestation from seven hydropic and 10 nonhydropic fetuses affected by rhesus isoimmunization, and the fetal plasma albumin, plasma total protein, and hemoglobin concentrations were determined. All fetuses with sonographic evidence of hydrops had a hemoglobin of 3.8 gm/dl or less, whereas all but one of those without hydrops had a hemoglobin greater than 4.0 gm/dl. The plasma total protein was less than 2 standard deviations below the mean of the normal range in all hydropic fetuses and in six of 10 of those without hydrops. Hypoalbuminemia was found in six of the seven hydropic fetuses and in two of the nonhydropic fetuses. Ascitic fluid total protein and albumin concentrations were also determined in four hydropic fetuses, and the values in three were found to be more than 50% of the corresponding plasma levels. (AM J OBSTET GYNECOL 1985;152:341-4.)

Key words: Fetoscopy, rhesus isoimmunization, hydrops pathophysiology

The pathophysiology of hydrops in the fetus severely affected by rhesus disease remains obscure. Theories offered in explanation of this process include heart failure as a consequence of profound fetal anemia, increased capillary permeability from the chronic tissue hypoxia of severe anemia, portal and umbilical venous hypertension caused by distortion of liver parenchyma with erythropoietic tissue, and the decreased colloid oncotic pressure of hypoproteinemia that results from liver dysfunction and/or reduced placental transfer of protein precursors.[1-5]

Investigation of these theories by examination of the hydropic neonate is limited by the attempt to discern from the end-stage of the process what the sequence of antecedent events may have been, as well as by the modifications of findings produced by intrauterine transfusion therapy. The development of a fetoscopic technique for sampling pure fetal blood permits biochemical and hematologic data to be obtained at the time of diagnosis of fetal hydrops before transfusion has been performed. This report presents pretransfusion plasma albumin, plasma total protein, and hemoglobin values in seven hydropic and 10 nonhydropic fetuses affected by rhesus isoimmunization, and ascitic fluid analysis for albumin and total protein in four hydropic fetuses.

Patients and methods

Fetoscopic sampling of pure fetal blood[6, 7] was performed in 17 severely rhesus-isoimmunized pregnant women at 18 to 25 weeks' gestation. The patients were referred for fetoscopic intravascular blood transfusion[8, 9] from several centers in the United Kingdom and other countries. These women had had a total of 82 previous pregnancies which resulted in 24 abortions, 23 intrauterine deaths, 10 neonatal deaths, and 25 surviving children. According to Whitfield's classification[10] on the outcome of previous rhesus-affected pregnancies (A = not affected; B = alive, no exchange transfusion; C = alive, at least one exchange transfusion; D = at least one rhesus-related death), 14 patients belonged in group D, two in group C, and one in group B.

In their present pregnancies, all patients, including 10 who underwent plasmapheresis, had high rhesus antibody levels (mean 59 IU/ml; range, 5 to 200 IU/ml), and in seven cases there was real-time ultrasonographic evidence of hydrops fetalis (fetal skin edema and ascites with or without associated pericardial and pleural effusions). The amniotic fluid optical density deviations at 450 nm wave length (ΔOD_{450}), at the time of fetoscopy, are shown in Table I.

All the fetuses had several intravascular blood transfusions (range, one to 5; mean, three) and survived. The data in this study were derived from the pretransfusion samples obtained at the first fetoscopy.

Samples of pure fetal blood were obtained from an umbilical cord artery and collected in isotonic ethylenediaminetetraacetic acid (EDTA) solution (150 μl of

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Table I. Status of disease and results of fetal blood sampling in 17 patients with rhesus isoimmunization

						Fetal		
Case No.	*Gestational age (wk)*	*Obstetric history**	*Maternal anti-D (IU/ml)*	*Amniotic fluid ΔOD at 450 nm*	*Ultrasound scan findings*	*Hemoglobin (gm/dl)*	*Plasma total protein (gm/L)*	*Plasma albumin (gm/L)*
1	18	D	200†	0.127	Hydrops	2.0	26	18
2	20	B	21†	0.310	Hydrops	3.6	28	17
3	21	D	76	0.285	Hydrops	3.3	27	17
4	22	D	33†	0.350	Hydrops	3.7	22	18
5	22	D	39	0.415	Hydrops	2.9	20	14
6	23	D	200†	0.359	Hydrops	3.4	28	17
7	25	D	40	0.644	Hydrops	3.8	35	18
8	19	D	89†	0.206	No hydrops	2.4	30	21
9	20	D	84	0.440	No hydrops	6.6	24	20
10	20	D	60†	0.210	No hydrops	6.6	25	17
11	20	C	5†	0.209	No hydrops	11.3	35	18
12	22	D	52†	0.301	No hydrops	4.7	25	20
13	22	D	28	0.359	No hydrops	9.0	34	26
14	22	D	34†	0.265	No hydrops	5.0	32	19
15	23	C	9	0.108		12.0	31	22
16	23	D	12†	0.375	No hydrops	9.2	28	22
17	23	D	21	0.415	No hydrops	5.3	31	20

*According to Whitfield's classification. See text.

†Patients undergoing plasmapheresis.

blood) and heparin solution (1 ml of blood). The fetal hemoglobin (gm/dl) was determined in the EDTA sample by means of a Coulter "S Plus" electronic blood cell counter, and plasma (heparin sample) albumin (gm/L) and total protein (gm/L) were measured on a Cobas Bio centrifugal analyzer (Roche Diagnostics) by a modified turbimetric technique.[11]

In four hydropic fetuses, the ascitic fluid total protein and albumin concentrations were also determined and compared with the corresponding plasma values. Clean samples of ascitic fluid (5 ml) were obtained by paracentesis through a specially made 20 gauge "Tuohy" needle passed down the side arm of the fetoscope cannula. In two of these cases the paracentesis was performed at the time of a second fetoscopy, because the fetuses did not have ascites at the first fetoscopy, 3 weeks previously.

Results

The gestational age at the time of fetoscopy and the status of the disease, together with the fetal hemoglobin, plasma total protein, and albumin levels are shown in Table I.

All fetuses with sonographic evidence of hydrops had a hemoglobin of 3.8 gm/dl or less, whereas all but one of those without hydrops had a hemoglobin greater than 4.0 gm/dl. The normal range of hemoglobin (mean + 2 SD), established from samples of blood obtained fetoscopically in 62 normal fetuses at 18 to 24 weeks' gestation, is 12.1 ± 2.4 gm/dl.[12]

The individual values of plasma total protein and albumin obtained in the 17 fetuses affected with rhesus isoimmunization are plotted in Fig. 1, *A* and *B*, respectively, against the normal ranges for gestation constructed from 194 normal control subjects.[13] The plasma total protein was below the mean −2 SD in all hydropic fetuses and in six of 10 fetuses without hydrops. Similarly, hypoalbuminemia was found in six of the seven hydropic fetuses and two of the nonhydropic ones.

The fetal plasma and ascitic fluid total protein and albumin concentrations in the four hydropic fetuses, in whom paracentesis was undertaken at the time of fetoscopy, are shown in Table II. In three cases the ascitic fluid levels were more than 50% of the corresponding plasma levels.

Comment

The consistently low values of plasma total protein and albumin concentrations found in the hydropic fetuses of the present study appear to verify a role of hypoproteinemia in the pathophysiology of rhesus hydrops.

Hypoproteinemia may result from hemodilution, decreased synthesis, or abnormal loss. Supporting evidence for extravascular loss of protein through an endothelial defect, possibly of hypoxic origin, is found in the relatively high total protein and albumin concentrations present in the ascitic fluid of those hydropic fetuses in whom this was evaluated. These protein levels are higher than would be anticipated as a result of transudation in the ascites of isolated portal hypertension or cardiac failure.[14] Concomitantly, evidence for decreased protein synthesis can be inferred from the

Table II. Comparison of total protein and albumin concentrations in the plasma and ascitic fluid of four fetuses with rhesus hydrops

Case No.	Gestational age (wk)	*Total protein (gm/L)* Plasma	*Total protein (gm/L)* Ascitic fluid	*Albumin (gm/L)* Plasma	*Albumin (gm/L)* Ascitic fluid
2*	20	28	15	17	9
7*	25	35	6	18	4
10†	23	36	20	20	15
13†	25	36	24	24	18

*Ascites found at first fetoscopy.

†Ascites found at second fetoscopy; no ascites at first fetoscopy.

hypoproteinemia found in six of the 10 nonhydropic fetuses with rhesus hemolytic anemia. None of these fetuses presented serous effusions as potential sites of protein loss. Although we cannot exclude hemodilution by direct evidence in these fetuses, Phibbs et al.[5] did not find a trend to increased blood volume in erythroblastotic newborn infants even in the presence of hydrops.

Bowman[4] has suggested that the development of ascites in rhesus disease is the result of portal and umbilical hypertension produced by distortion of the hepatic parenchyma with islets of erythropoiesis. With progression of this erythropoietic intrusion, there is impaired protein synthesis in the liver that results in hypoproteinemia. As the hypoproteinemia becomes more severe, generalized edema (hydrops) ensues. Although the evidence of decreased protein production in the erythroblastotic fetuses of our study is consistent with this sequence of events in hydrops formation, the data from ascitic fluid analysis suggest that transendothelial leakage of protein is also an important factor in the development of hypoproteinemia.

Consistent with the theory of hypoxic endothelial damage in the etiology of rhesus hydrops is the uniform finding in our study of severe anemia in the hydropic fetuses, all of whom had hemoglobin levels of less than 4 gm/dl. Although exceptions to the usual association of severe anemia and hydrops in rhesus-affected newborn infants have been reported, the cited cases have generally undergone previous intrauterine transfusion therapy, which may account for the discrepancy with our findings in untreated fetuses.[5, 15] Although all of the hydropic fetuses in the present study were severely anemic, equally severe anemia was identified in one nonhydropic fetus. These relationships of severity of anemia to the presence or absence of hydrops were also found in an additional group of patients whose fetal hematologic indices were reported recently from our institution.[12] We postulate that, in addition to a critical level of anemia for the occurrence of hydrops, the duration of severe anemia may also be a determinant. Thus, failure to produce hydrops by induction of acute anemia in an animal model[16, 17] contrasts with the well-recognized spontaneous occurrence of hydrops in α-thalassemia and instances of chronic fetomaternal hemorrhage or twin transfusion syndrome, conditions characterized by severe anemia of chronic duration.[18]

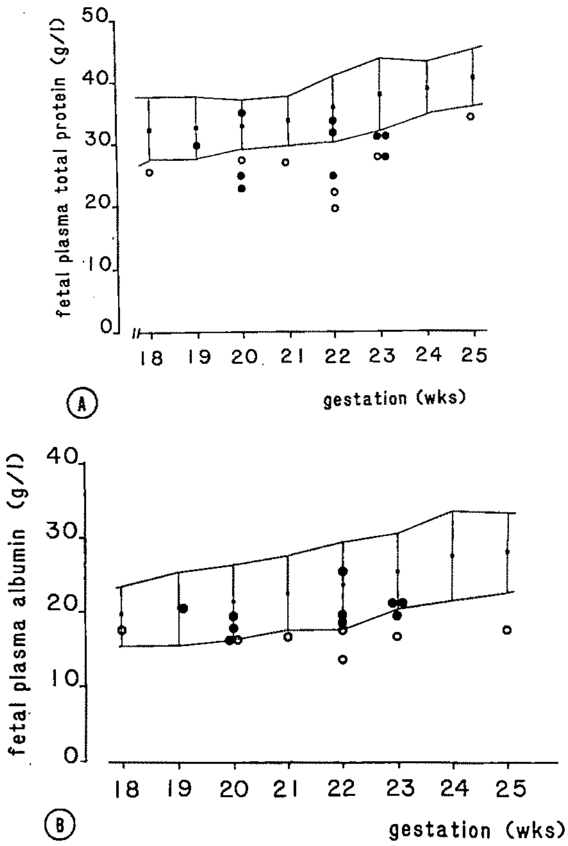

Fig. 1. Fetal plasma total protein *(A)* and albumin *(B)* in seven hydropic (○) and 10 nonhydropic (●) fetuses affected by rhesus isoimmunization, plotted against the reference values (mean ± 2 SD) constructed from 194 normal control subjects.

In this study, severe anemia and hypoproteinemia were found in all fetuses with rhesus hydrops. We think that severe chronic anemia, probably acting through tissue hypoxia, is the most likely factor in initiating the hydropic process. We are at present testing this hypothesis by studying the blood gases of these fetuses. Hypoproteinemia that results from a combination of hypoxia-induced endothelial leakage and decreased production appears to be an important factor in the abnormal shift of fluid which occurs.

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The role of transferrin and ferritin in the fetal-maternal-placental unit

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The rapidly growing human fetus requires a large supply of iron, which is obtained from the iron stores of the mother. Iron is transported from mother to fetus against a concentration gradient. The placenta plays a key role in regulating the supply of iron in the fetus. In both anemic and nonanemic patients serum ferritin levels decreased and total iron-binding capacity increased as gestation progressed. The total iron-binding capacity is higher in maternal than in umbilical cord blood at delivery; this suggests that little or no ferritin or transferrin is transferred from mother to fetus. Mother and fetus appear to have independent systems controlling iron metabolism. Transferrin was localized on the site facing the intervillous space, on the surface of the microvilli of the syncytiotrophoblasts. The removal of transferrin from the surface of the trophoblast by thiocyanate and its rebinding were demonstrated. Ferritin was shown to be present in all layers of the trophoblast and especially in the syncytiotrophoblast. (AM J OBSTET GYNECOL 1985;152:344-50.)

Key words: Iron transport, placenta, ferritin, transferrin, immunochemistry, iron requirement of fetus

The ubiquitous element iron plays key roles in oxygen transport, in electron transport, and in many enzymatic reactions. Transferrin, a protein that transports iron, is present in the yolk sac of the early embryo in a form that is immunologically similar to that present in the sera of adults.[1]

The developing human fetus has an immense demand for iron, requiring 250 to 300 mg of iron during gestation.[2] Iron is transported one way from maternal blood to the fetus. The placenta, in addition to transporting iron from mother to fetus against a concentration gradient,[3] serves as a storage depot for iron.

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In the present studies the authors examined the amounts and dynamics of transferrin and ferritin in the fetal-maternal-placental unit by means of biochemical and immunohistologic methods.

Material and methods

Determination of hemoglobin volume, serum ferritin level, and total iron-binding capacity in the blood of the pregnant woman at each stage of gestation. With 113 normal pregnant women at each stage of gestation as subjects, hemoglobin volume was determined by the cyanmethemoglobin method, serum ferritin level by radioimmunoassay (Spac-Ferritin Kit, Daiichi Radioisotope) with use of antihuman liver ferritin antibody, and total iron-binding capacity by use of the Resomat-Fe Kit (Daiichi Radioisotope).

Determination of serum iron level, serum ferritin level, and total iron-binding capacity in maternal blood and umbilical blood at delivery. From 35 normal parturient women, cubital venous blood was drawn at delivery and umbilical cord venous blood was collected immediately after delivery. The serum iron concentration of each sample was determined by the basophenanthroline method; and serum ferritin level and total iron-binding capacity were measured as described above.

The localization of transferrin in placental villous tissue. A small cube of villous tissue was cut from the placenta immediately after normal term delivery, rinsed with physiologic saline solution to remove blood, fixed in a periodate-lysine paraformaldehyde solution for 2 to 4 hours, and embedded in paraffin for sectioning and observation under light microscopy.

For electron microscopy the sample was frozen at −60° C, and sections were cut. Thereafter transferrin was identified by the enzyme-conjugated antibody method (indirect method) with use of the method of Nakane and Kawaoi.[4] For the first antibody, antihuman liver transferrin rabbit IgG: whole (Dako Corporation) was used. For the second antibody, peroxidase-labeled rabbit IgG and goat IgG: whole (Japan Antibody Institute) was used. For the control, phosphate-buffered saline solution or nonimmunized rabbit serum was used in place of the first antibody, the nonspecific reaction was checked, and the specificity of the localization of antibody was confirmed. Thus the localization of transferrin in placental villous tissue was observed both by light microscopy and by electron microscopy (Fig. 1).

Small pieces of villous tissue were extracted immediately from the placenta obtained after normal term delivery, rinsed to remove blood, and incubated for 10 minutes in a solution of 0.5 mol/L of ammonium thiocyanate according to the method of Galbraith et al.[5] (Fig. 2). Thereafter a part of the sample was fixed in 10% formalin, and the remainder was rinsed in a buffer solution, incubated again in the sera of the maternal blood collected at delivery, rinsed again in a buffer solution, and fixed in formalin. Each sample was treated with the enzyme-conjugated antibody method described above, and the localization of transferrin was observed by light microscopy.

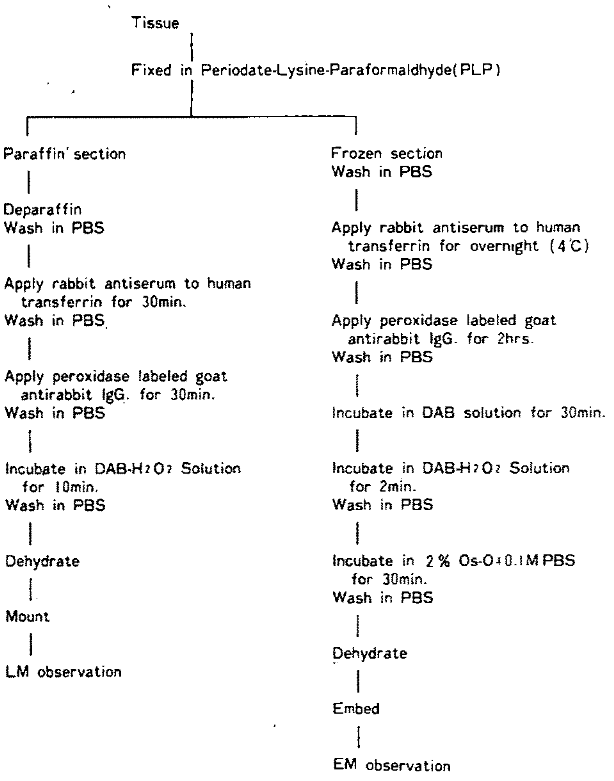
Tissue
Fixed in Periodate-Lysine-Paraformaldhyde(PLP)
Paraffin section
Deparaffin
Wash in PBS
Apply rabbit antiserum to human transferrin for 30min.
Wash in PBS
Apply peroxidase labeled goat antirabbit IgG. for 30min.
Wash in PBS
Incubate in DAB-H2O2 Solution for 10min.
Wash in PBS
Dehydrate
Mount
LM observation
Frozen section
Wash in PBS
Apply rabbit antiserum to human transferrin for overnight (4°C)
Wash in PBS
Apply peroxidase labeled goat antirabbit IgG. for 2hrs.
Wash in PBS
Incubate in DAB solution for 30min.
Incubate in DAB-H2O2 Solution for 2min.
Wash in PBS
Incubate in 2% Os-O4 0.1M PBS for 30min.
Wash in PBS
Dehydrate
Embed
EM observation

Fig. 1. Localization of transferrin by the peroxidase-labeled antibody method (indirect enzyme-conjugated antibody method).

Localization of ferritin in placental villous tissue. The enzyme-conjugated antibody method (indirect method) was performed similarly on placental villous tissue obtained at normal term delivery. For the first antibody, antihuman placental rabbit IgG: whole (Hoechst Corporation) was used. For the second antibody, peroxidase-labeled antirabbit IgG and goat IgG, F(ab')2: whole (Cappel Corporation) was used. The control test was similarly performed with transferrin, and the localization of ferritin was observed by light microscopy.

Determination of ferritin concentration in placental villous tissue. Thirty samples of placentas at each stage of gestation were used. After the decidua, the fetal membranes, and the umbilical cord were removed, the placenta was cut into small pieces and rinsed several times in physiologic saline solution to remove blood. The fetal vasculature was also removed as completely as possible. To the villous tissue thus obtained, 1.5 times as large an amount of distilled water was added, and the placenta was homogenized. A part of the homogenate was used for protein determination, and the remainder was centrifuged at 3000 gm for 30 minutes.

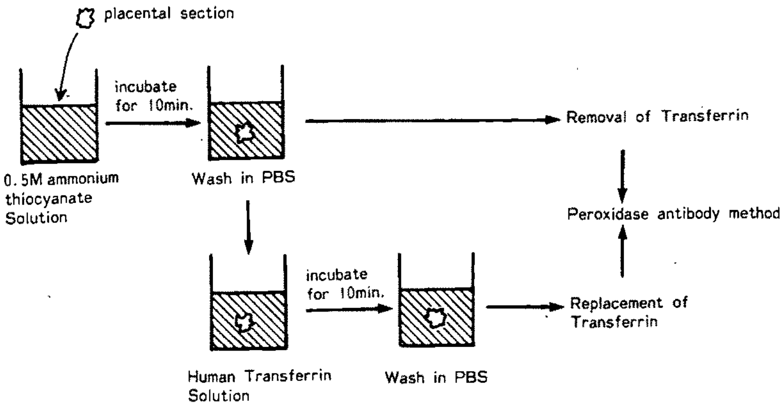
placental section
incubate for 10min.
0.5M ammonium thiocyanate Solution
Wash in PBS
Removal of Transferrin
Peroxidase antibody method
incubate for 10min.
Replacement of Transferrin
Human Transferrin Solution
Wash in PBS

Fig. 2. Removal and replacement of transferrin in the trophoblast.

Table I. Serum ferritin and related hematologic values in pregnant women

Stage of gestation	*No. of women*	*Serum ferritin (ng/ml)*	*Hemoglobin (gm/dl)*	*Total iron-binding capacity (μg/dl)*
Nonanemic group (hemoglobin $\geq$11 gm/dl)				
First trimester	32	34.1 ± 19.0	12.3 ± 0.7	394 ± 51
Second trimester	17	22.9 ± 12.2	11.8 ± 0.7	434 ± 81
Third trimester	17	19.4 ± 11.7	11.7 ± 0.8	443 ± 53
Anemic group (hemoglobin <11g/dl)				
First trimester	10	15.1 ± 7.8	9.9 ± 1.1	464 ± 11
Second trimester	15	10.2 ± 6.7	9.9 ± 0.6	501 ± 52
Third trimester	22	5.2 ± 2.2	9.8 ± 1.1	509 ± 82

Values are expressed as mean ± SD.

Table II. Iron, ferritin, and total iron-binding capacity of maternal and fetal blood at delivery (n = 35)

	Maternal blood	*Cord blood*
Iron (μg/dl)	59.8 ± 26.2*	161.5 ± 42.1*
Ferritin (ng/ml)	9.6 ± 7.2*	160.5 ± 67.2*
Total iron-binding capacity (μg/dl)	495.2 ± 100.3*	177.7 ± 33.9*

*$p < 0.05$. Values are expressed as mean ± SD.

The supernatant fraction was heated at 80° C for 10 minutes, then cooled suddenly, and again centrifuged at 3000 gm for 30 minutes. The supernatant thus obtained was used for the determination of ferritin by the ferritin test (Research Laboratories, Yamonouchi Pharmaceutical) with the use of antihuman placental ferritin antibody.

Protein concentration was determined by the method of Lowry et al.[6]

Results

Hemoglobin volume, serum ferritin level, and total iron-binding capacity in the blood of the pregnant woman at successive stages of gestation. Pregnant women at each stage of gestation were classified into a nonanemic group if hemoglobin volume was $\geq$11 gm/dl and into an anemic group if hemoglobin volume was <11 gm/dl. In both anemic and nonanemic patients the serum ferritin level decreased gradually with the progress of gestation whereas the total iron-binding capacity increased gradually with gestation (Table I).

Serum iron level, serum ferritin level, and total iron-binding capacity in maternal blood and umbilical blood at delivery. Both the serum iron level and the serum ferritin level in umbilical blood were greater than in maternal blood, whereas the total iron-binding capacity in maternal blood was significantly greater than that in umbilical blood ($p < 0.05$) (Table II).

There was no significant correlation between the concentrations of any of these constituents in maternal and fetal blood.

Localization of transferrin in placental villous tissue. Deposits of reaction products indicating the localization of transferrin were detected by light microscopy on the site facing the intervillous space over the surface of the trophoblast and by electron microscopy on the surface of microvilli of syncytiotrophoblasts (Figs. 3 and 4).

In the incubation experiments conducted simulta-

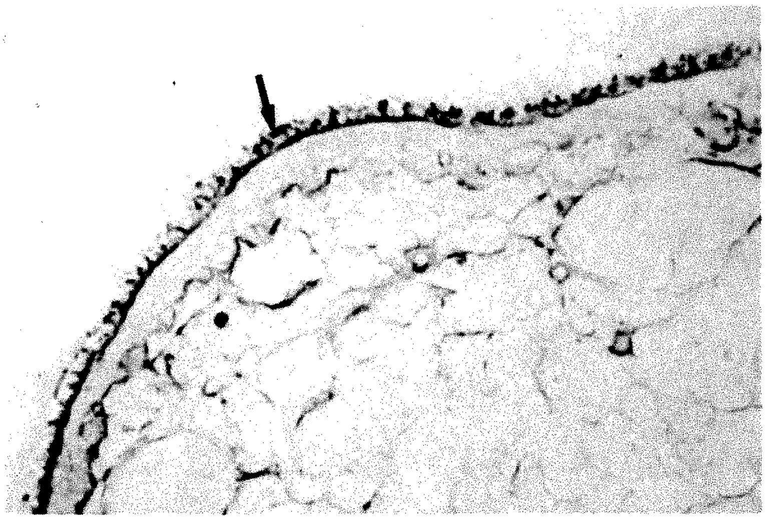

Fig. 3. Localization of transferrin in placental villous tissue (×400). Reaction products of transferrin are found on the surface of the trophoblasts *(arrow)*.

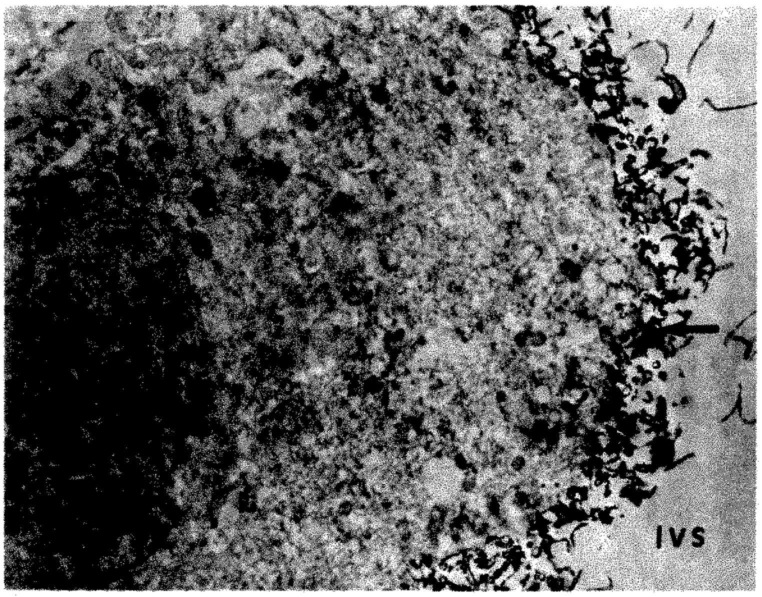

Fig. 4. The localization of transferrin in placental villous tissue (×7200). Reaction products of transferrin are found on the surface of microvilli of syncytiotrophoblasts *(arrow)*. *N*, Nucleus; *IVS*, intervillous space.

neously, the removal of transferrin from the surface of trophoblasts by treatment with thiocyanate and the subsequent rebinding of transferrin to the surface of trophoblasts were observed (Fig. 5).

Localization of ferritin in placental villous tissue. Deposits of reaction products indicating the localization of ferritin were found in all layers of the trophoblast and especially in the syncytiotrophoblast (Fig. 6).

Ferritin concentrations in placental villous tissue. The concentration of ferritin in placental villous tissue increased as gestation progressed from 0.07 ± 0.03 μg/mg protein in the first trimester to 0.18 ± 0.03 μg/mg protein in the second and 0.25 ± 0.09 μg/mg protein in the third trimester (Table III and Fig. 7).

Comment

Pommerenke[7] observed that radioactive iron administered to a pregnant woman was transferred to the fetus very quickly. In rabbits and in humans iron transport is one-way from the mother to the offspring, and in the latter stage of gestation iron is transferred against a concentration gradient.[3] In humans the amount of iron passing through the placenta increases as gestation progresses.[8] In rabbits iron is taken up by the placenta even if the umbilical cord is ligated and the traffic between the placenta and the fetus is interrupted.[9]

In contrast, Woehler[10] found that a high dose of iron administered to pregnant rats did not result in an excessive amount of iron in the fetus.

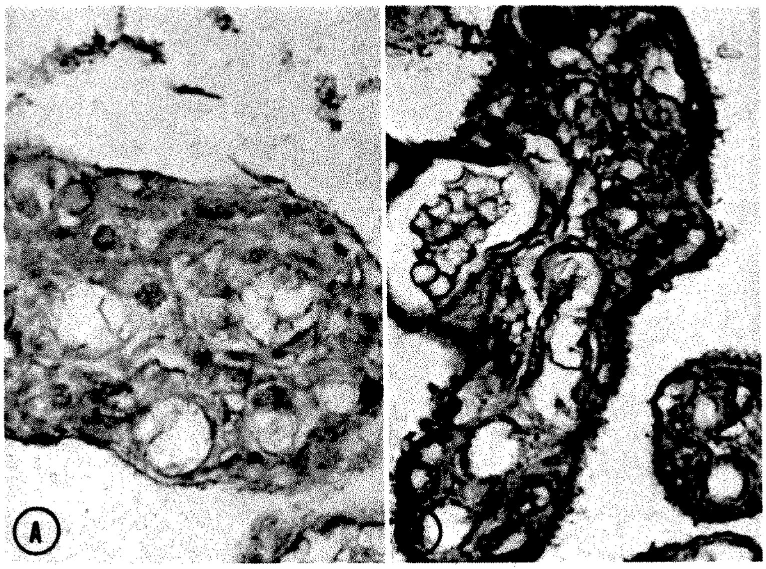

Fig. 5. *A*, Removal of transferrin with use of ammonium thiocyanate. Reaction products of transferrin are not visible on the surface of the trophoblasts. The surface seems smooth (×200). *B*, Replacement of transferrin by maternal serum transferrin. Reaction products of transferrin are evident on the surface of the trophoblasts.

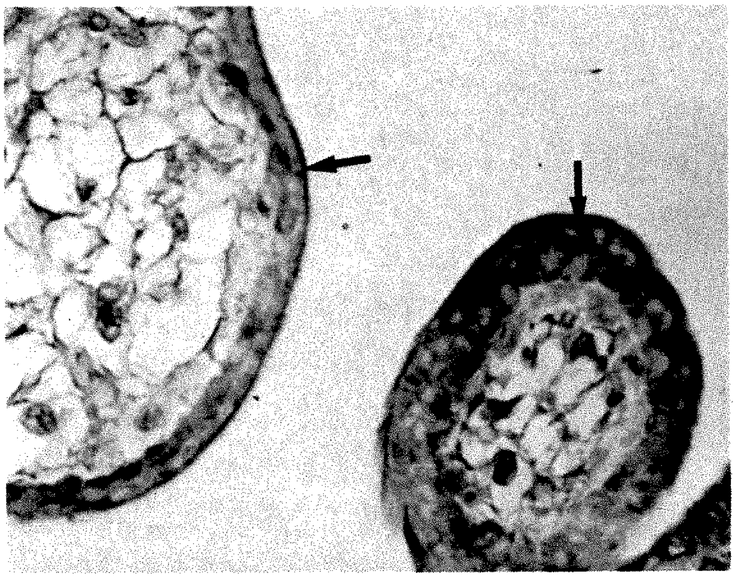

Fig. 6. The localization of ferritin in placental villous tissue (×200). Reaction products of ferritin are present in all layers of the trophoblasts, especially near the surface *(arrows)*.

Table III. Concentration of ferritin in placental tissue at first, second, and third trimester

Stage of gestation	*First trimester*	*Second trimester*	*Third trimester*
No. of cases	10	5	15
Ferritin content (μg/mg of protein)	0.07 ± 0.03*	0.18 ± 0.03*	0.25 ± 0.09*

*$p < 0.05$. Values are expressed as mean ± SD.

In animals with hemochorial placentas such as the human, rabbit, and rat, iron transport from mother to fetus may be one-way. Some specific mechanism may actively take up iron needed by the fetus against a concentration gradient and control the iron concentration so that there is no excess of iron in the fetus.

Serum ferritin[11] has been considered to reflect the amount of iron stored in the body. Its concentration characteristically decreases as gestation progresses. The concentration of maternal hemoglobin is also greatly reduced in the latter part of pregnancy even in women who were not anemic.

These findings indicate that iron is mobilized from the stored iron pool in the mother as gestation progresses in order to meet the increasing demands for iron for hematopoiesis in the fetus and placenta. The amount of stored iron decreases. Latent iron deficiency is probably always present in the mother, even if the hemoglobin level remains within the normal range.

At delivery the umbilical cord blood had a significantly higher content of serum iron than the maternal blood. This provides evidence that at least in the terminal stage of gestation iron is actively transported from mother to child against a concentration gradient. The umbilical cord blood also contains a significantly higher amount of serum ferritin than does the maternal blood. The total iron-binding capacity was significantly higher in the maternal blood than in the umbilical cord blood. This indicates that there is little or no transfer of ferritin and transferrin between mother and child. The mother is in a state of iron deficiency, with low serum ferritin level and high total iron-binding capacity, and the fetus is in a state of iron sufficiency, with high serum ferritin level and low iron-binding capacity. Thus iron storage in the mother and iron metabolism in the fetus are not directly related. This suggests that mother and fetus have independent systems for the control of iron metabolism. The transport of iron from mother to fetus by the placenta may be under some separate controlling mechanism.

Iron is present in maternal serum mainly bound to transferrin and ferritin. When a large volume of ferritin was loaded on placental villous tissue, ferritin was incorporated into the placenta by pinocytosis in the trophoblasts.[12] However, the amount of serum ferritin in maternal blood is small, and its iron content is also very small. Even though the turnover of iron bound to ferritin is very rapid, the significance of serum ferritin as the source of iron to the fetus may be minimal. The major source of iron to the fetus is the iron bound to transferrin in maternal blood.

Our present studies of the localization of transferrin in placental villous tissue by the enzyme-conjugated antibody method confirmed its localization on the microvilli of the syncytiotrophoblast. The subsequent incubation experiments showed that this was identical to the transferrin in maternal blood.

Receptors for transferrin are present on the surface of placental villous epithelial cells.[5] This may indicate that transferrin in maternal blood binds specifically to the surface of the microvilli of syncytiotrophoblasts as the first step in the mechanism by which iron is transported across the placenta.

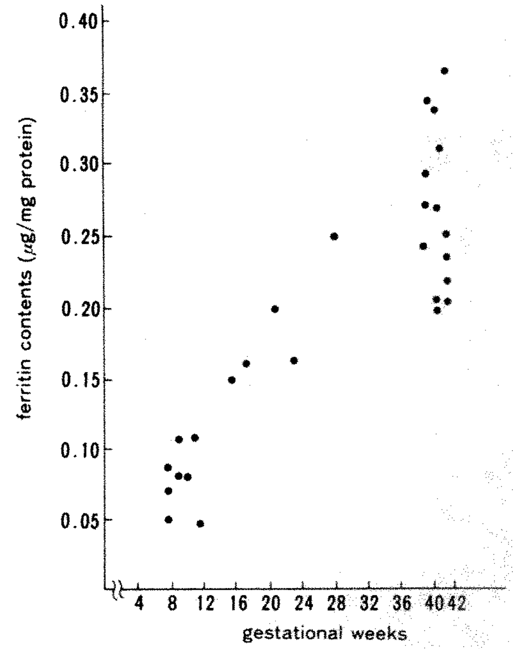

Fig. 7. Concentration of ferritin in placental tissues.

The process by which iron is incorporated from the transferrin in maternal blood bound on the surface of microvilli into the cytoplasm of the syncytiotrophoblast remains unclear. Harding et al.[13] demonstrated in rat reticulocytes that the transferrin bound to transferrin receptors on the cell membrane was incorporated into the cytoplasm by pinocytosis. Thus they demonstrated the existence of receptor-mediated endocytosis, both biochemically and morphologically. We suggest that a similar mechanism exists on the syncytiotrophoblast of the placenta.

It has been maintained[2] that the amount of transferrin transported from maternal to fetal blood is very small compared to the amount of iron transported. Therefore the transferrin incorporated into syncytiotrophoblasts is considered to transfer iron to other mediators rather than being transferred completely across the placenta to the fetal blood. Oski and Naiman[14] reported that iron bound to transferrin in maternal blood was incorporated into trophoblasts first and then was bound to ferritin. Our experiments indicate that the ferritin concentration in the placenta increased with the progress of gestation. The amount of iron passing daily through the placenta is increased as gestation progresses.[9] Our experiments show that ferritin is localized in the entire trophoblast.

These findings indicate that the amount of ferritin within the trophoblasts rose with the increase in iron transport and that ferritin plays an important role in iron transport across the placenta. Ferritin consists of H and L subunits. Acidic ferritin, in which the H subunit is dominant, can incorporate iron more efficiently and can meet the demand for iron ions more rapidly. Basic ferritin, in which the L subunit is dominant, is more stable metabolically and is associated with the storage of iron. The ratio of H and L subunits varies with the amount of iron in the tissue. When an adequate amount of iron is present, the L subunit becomes dominant, whereas in iron deficiency the H subunit becomes dominant. Ferritin may be involved not only in the storage of surplus iron but also more actively in iron metabolism than had been considered previously.

The ferritin in human placenta is acidic ferritin with the H subunit dominant.[15] Acidic ferritin characteristically incorporates iron efficiently and responds quickly to the demands for iron. When an excess amount of iron was administered to rats, their placenta ferritin became basic and the L subunit became dominant. It can be postulated from these findings that human placental ferritin has the two functions of transporting iron when it is deficient and of storing it when it is present in excess. Ferritin acts as a safety valve in iron metabolism, regulating the transport of iron between mother and fetus and ensuring a constant supply of iron to the fetus.

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Effects of maternal oxygen administration on fetal oxygenation during reductions in umbilical blood flow in fetal lambs

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In 11 chronically catheterized fetal lambs (123 ± 6, mean ± SD, days of gestation; term = 147 days), we measured fetal oxygen delivery and oxygen consumption before and during reductions in umbilical blood flow ($\dot{Q}_{umb}$). $\dot{Q}_{umb}$ was reduced by inflation of a balloon occluder located just proximal to the origin of the common umbilical artery. Measurements were made while the unanesthetized maternal sheep received either room air or 100% oxygen to breathe. In oxygen-treated fetuses, oxygen concentrations in umbilical venous blood (Cuv_{O_2}) and arterial blood (Ca_{O_2}) were increased over a wide range of $\dot{Q}_{umb}$ when compared with those of room air–treated fetuses. Because of these responses, fetal oxygen delivery ($Do_2 = \dot{Q}_{umb} \cdot Cuv_{O_2}$) and oxygen consumption [$\dot{V}o_2 = \dot{Q}_{umb}(Cuv_{O_2} - Ca_{O_2})$] were greater in oxygen-treated fetuses than in room air–treated fetuses during episodes of reduced $\dot{Q}_{umb}$. In oxygen-treated fetuses, $\dot{V}o_2$ decreased from normal levels only when $\dot{Q}_{umb}$ was ≤ 75 ml/min/kg of fetus, whereas in room air–treated fetuses $\dot{V}o_2$ decreased at $\dot{Q}_{umb} \leq 150$ ml/min/kg. Our data indicate that oxygen administration to the pregnant sheep increases oxygen delivery to the fetus during times of reduced umbilical perfusion and that this supplemental oxygen supply provides an oxygen reserve with which the fetus can maintain oxidative metabolism. These data may be relevant to those clinical conditions, such as umbilical cord compression in labor, that are associated with reductions in umbilical blood flow. (AM J OBSTET GYNECOL 1985;152:351-8.)

Key words: Umbilical blood flow, fetal oxygenation, oxygen delivery

Reductions in umbilical blood flow result in decreases in the total delivery of oxygen to the fetus.[1, 2] Such decreases can adversely affect fetal oxygen consumption if the delivery of oxygen is inadequate for the demands for oxygen. Recent experiments on fetal lambs have shown that when umbilical blood flow and thus fetal oxygen delivery are reduced more than approximately 40%, fetal oxygen consumption decreases.[2] Since under these conditions oxygen consumption is a function of oxygen delivery, any measure taken to increase fetal oxygen delivery during reductions in umbilical blood flow should restore fetal oxidative metabolism toward normal. Administration of supplemental oxygen to the mother may be one such beneficial measure.

Maternal oxygen administration results in increases in the oxygen tension and oxygen concentration of fetal blood.[3-6] Although maternal oxygen administration increases oxygen availability to the fetus with a normal umbilical blood flow,[4] the effect of oxygen treatment on the fetus with a reduced umbilical blood flow has not been determined. The purpose of our experiments was to measure the effects of maternal oxygen administration on fetal oxygen delivery and oxygen consumption before and during reductions in umbilical blood flow. We wanted to test the hypothesis that fetuses whose mothers received supplemental oxygen would tolerate greater reductions in umbilical blood flow before fetal oxygen consumption fell than fetuses whose mothers breathed only air.

Methods

Preparation of animals. We surgically prepared 11 pregnant sheep of gestational ages ranging from 110 to 130 days (term = 147 days). After an epidural or spinal anesthetic (tetracaine hydrochloride, 1%) was administered to the mother, we inserted a catheter into a maternal femoral artery, then opened the maternal abdomen and pregnant uterine horn, and placed catheters into two fetal hind limb arteries and a vein.[7] These latter catheters were advanced into both femoral arteries and a femoral vein. Anesthesia for catheter placements in the fetus was provided by lidocaine hydrochloride, 0.5%, administered locally. A balloon-tipped occluder catheter (Fogarty Embolectomy, No. 3) was also placed into a hind limb artery and was advanced

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into the descending aorta so that the balloon was 1 to 2 cm cephalad to the origin of the common umbilical artery.[7] After closing the uterine incision, we made a new incision over the area of the fetal abdomen and inserted a catheter into the common umbilical vein.[8] An open-ended catheter was left in the amniotic sac. All incisions were closed and catheters were brought out subcutaneously to the ewe's flank where they were stored in a pouch. Two to four days after operation, we studied the fetuses of the unanesthetized sheep as the sheep stood unrestrained in a transport cage.

Experimental protocol. In each fetus, we measured the effects of maternal oxygen administration on fetal oxygen delivery, oxygen consumption, and acid-base balance at various randomly determined levels of umbilical blood flow. We made a total of 49 measurements in the 11 fetuses studied. Of the 49 observations, 25 were made in sheep breathing room air, and the remaining 24 measurements were made in sheep receiving 100% oxygen for >20 minutes via a vented, clear plastic bag that enclosed the sheep's head. Oxygen was administered into the bag at a flow rate >25 L/min to reduce the problem of carbon dioxide retention in the ewe (maternal arterial P_{CO_2} did not change significantly when the sheep received 100% oxygen to breathe). For each measurement, we selected at random whether the sheep breathed room air or 100% oxygen.

To change umbilical blood flow, we inflated the balloon-tipped occluder in the fetal descending aorta. Umbilical blood flow was altered for 4 to 8 minutes, during which time fetal heart rate and arterial blood pressure were continuously monitored and recorded. In the first four fetuses studied, we measured femoral arterial and umbilical venous blood P_{O_2} values serially at 1- to 2-minute intervals during the reduced umbilical flow state. We found that a steady state in the blood P_{O_2} values (maximum variation ≤10%) was achieved only after umbilical flow had been reduced for ≥2 minutes. Therefore, in all fetuses studied, we altered umbilical blood flow for ≥2 minutes before any measurements of fetal oxygenation were made. For each such measurement, we withdrew 0.8 ml blood samples from the maternal femoral artery, umbilical vein, and fetal femoral artery for the analyses of blood gases, pH, base excess, oxygen concentration, and hematocrit. Blood samples were kept on ice until analyzed (always within 15 minutes). Immediately after obtaining the blood samples, we injected 1 to 2 × 10^6 microspheres (15 μm diameter, labeled with iodine 125, cerium 141, chromium 51, strontium 85, niobium 95, or scandium 46) into the fetal femoral vein while withdrawing a femoral arterial blood reference sample.[9] Microsphere injections and blood withdrawals had no effects on fetal arterial blood pressure or heart rate. At the completion of the blood withdrawal, we deflated the occluder and allowed the fetus sufficient time for heart rate, blood pressure, blood gases and pH, and oxygen concentration to return to normal. We then reduced umbilical flow to a new level and repeated the study. Measurements were also made on fetuses in which umbilical flow was not reduced. Each fetus was studied an average of four times (range, two to six). Total fetal blood volume withdrawn rduring the entire study did not exceed 30 ml, which represented <7% of estimated blood volume.[10] Hematocrit did not change significantly over the course of the experiment.

We measured blood and amniotic fluid pressures with Statham pressure transducers (P23Db) and heart rate with a cardiotachometer and recorded these continuously on a Beckman multichannel recorder (R611A). Blood gases, pH, and base excess were measured at 37° C for maternal blood and at 38° C for fetal blood with standard electrodes and a blood gas meter (Corning). Hematocrit was measured with the microcapillary technique. Blood oxygen concentration (total of oxygen bound to hemoglobin plus oxygen dissolved in plasma) was measured in duplicate with a Lex-O_2-Con oxygen analyzer.

Preparation of tissues and calculation of data. When the study was completed, the sheep and fetuses were killed with an overdose of sodium pentobarbital, and the fetuses and placentas were removed and weighed. Correct catheter locations were verified visually. The amounts of each radionuclide present in the placenta and in the arterial blood reference samples were measured with a well-type gamma scintillation counter (Model 1185, Searle Analytical) and a multichannel pulse-height analyzer (Ultima II, Norland). Nuclide isotope separation was performed by computer (Nova 3, Data General).[9] Arterial blood reference samples contained >1500 microspheres to ensure that the error in any flow measurement was <5% (95% confidence limits).[11]

We computed umbilical blood flow ($\dot{Q}_{umb}$) as follows[7, 9]:

$$\dot{Q}_{umb} = (cpm_{plac}/cpm_{ref}) \cdot \dot{Q}_{ref}$$

where cpm_{plac} = radioactive counts per minute in the placenta, cpm_{ref} = radioactive counts per minute in the arterial blood reference sample, and $\dot{Q}_{ref}$ = reference blood flow determined by calibrating the withdrawal pump. $\dot{Q}_{umb}$ was expressed as milliliters per minute per kilogram of fetal body weight.

We calculated fetal oxygen delivery (D_{O_2}) and oxygen consumption ($\dot{V}_{O_2}$) using modifications of the Fick principle[2, 4, 6]:

$$D_{O_2} = \dot{Q}_{umb} \cdot Cuv_{O_2}$$
$$\dot{V}_{O_2} = \dot{Q}_{umb}\,(Cuv_{O_2} - Ca_{O_2})$$

where Cuv_{O_2} = umbilical venous blood oxygen concen-

Table I. Effects of maternal oxygen administration on fetal heart rate, blood pressure, and acid-base balance during reductions in umbilical blood flow

		Umbilical blood flow ranges (ml/min/kg fetus)			
	Condition	*226-300*	*151-225*	*76-150*	*0-75*
n	RA	9	5	5	6
	O_2	4	8	7	5
Fetal heart rate (bpm)	RA	173 ± 11	167 ± 18	128 ± 10*	129 ± 6*
	O_2	186 ± 25	168 ± 18	135 ± 36*	128 ± 19*
Mean arterial blood pressure (mm Hg)	RA	54 ± 9	49 ± 8*	36 ± 13*	28 ± 14*
	O_2	53 ± 6	48 ± 9*	34 ± 10*	28 ± 10*
Umbilical venous blood					
Po_2 (mm Hg)	RA	30 ± 6	26 ± 3	28 ± 3	30 ± 7
	O_2	57 ± 8†	46 ± 16†	38 ± 3†	38 ± 13
Pco_2 (mm Hg)	RA	38 ± 3	38 ± 2	39 ± 1	41 ± 3
	O_2	39 ± 5	39 ± 4	38 ± 4	40 ± 5
pH	RA	7.44 ± 0.04	7.45 ± 0.04	7.41 ± 0.04	7.34 ± 0.08*
	O_2	7.42 ± 0.05	7.43 ± 0.03	7.43 ± 0.03	7.36 ± 0.06*
Arterial blood					
Po_2 (mm Hg)	RA	21 ± 4	18 ± 2*	14 ± 3*	11 ± 3*
	O_2	27 ± 3†	24 ± 5*†	16 ± 4*	11 ± 2*
Pco_2 (mm Hg)	RA	43 ± 3	44 ± 1	48 ± 3	54 ± 7*
	O_2	45 ± 4	45 ± 5	45 ± 5	53 ± 7*
pH	RA	7.40 ± 0.05	7.41 ± 0.04	7.35 ± 0.02*	7.26 ± 0.08*
	O_2	7.38 ± 0.03	7.38 ± 0.02	7.36 ± 0.02	7.29 ± 0.08*
Base excess (mEq/L)	RA	1 ± 2	2 ± 2	−1 ± 2	−4 ± 4*
	O_2	2 ± 1	0 ± 2	0 ± 2	−3 ± 1*

n = number of observations; values are means ± SD. RA = Room air; O_2 = 100% oxygen.
*$p<0.05$ within rows, compared with values obtained in umbilical flow range of 226 to 300 ml/min/kg.
†$p<0.05$ within columns, room air measurements versus 100% oxygen measurements.

tration and Ca_{O_2} = femoral (umbilical) arterial blood oxygen concentration, in milliliters of oxygen per deciliter of blood. Do_2 and $\dot{V}o_2$ were expressed as milliliters of oxygen per minute per kilogram of fetus.

Data analyses. We plotted the following dependent variables against umbilical blood flow: umbilical venous and arterial blood oxygen concentrations, umbilical venous-arterial oxygen concentration difference, fetal oxygen delivery, and fetal oxygen consumption. Data analyses were based on 49 measurements made in the 11 fetuses studied. Data (n = 25) obtained from animals breathing room air were analyzed separately from data (n = 24) obtained when mothers received 100% oxygen to breathe. We fit regression curves to each set of data by the least-squares method.[12] Linear, logarithmic, and power functions were all tested for best fit; the function selected as best describing each relationship had the greatest correlation coefficient associated with the least residual sum of squares. For each dependent variable plotted against umbilical flow, we compared the slopes and intercepts of the function describing the response seen in room air–treated fetuses with that describing oxygen-treated fetuses. When nonlinear equations fit the data best, data were linearly transformed before these comparisons were made. If either the slopes or the intercepts differed significantly, we used a two-way analysis of variance (with Dunnett's and Neuman-Keuls' tests) to identify where significant differences existed between fetuses treated with room air or 100% oxygen.[12] To perform this latter analysis, we divided the range of umbilical blood flow measurements into four equal parts: 226 to 300, 151 to 225, 76 to 150, and 0 to 75 ml/min/kg. For all analyses, p values <0.05 were used to indicate statistically significant differences.

Results

In the 11 animals studied, gestational age was 123 ± 6 days (mean ± SD) and maternal hematocrit was 26% ± 2%; fetal body weight was 2.7 ± 0.7 kg, and fetal hematocrit was 32% ± 4%. In sheep breathing room air, maternal arterial blood Po_2 was 89 ± 6 mm Hg and blood oxygen concentration was 12.5 ± 1.2 ml of oxygen per deciliter of blood. In sheep breathing 100% oxygen, arterial Po_2 increased to 302 ± 21 mm Hg, while oxygen concentration rose to 13.8 ± 1.0 ml of oxygen per deciliter of blood.

Table I shows the effects of maternal oxygen administration on fetal heart rate, mean femoral arterial blood pressure, blood gases, and acid-base balance during reductions in umbilical blood flow. Decreases in umbilical blood flow were associated with decreases in fetal heart rate and mean arterial blood pressure that were the same in the room air–treated and oxygen-treated animals. In room air–treated fetuses, reductions in umbilical blood flow did not affect umbilical

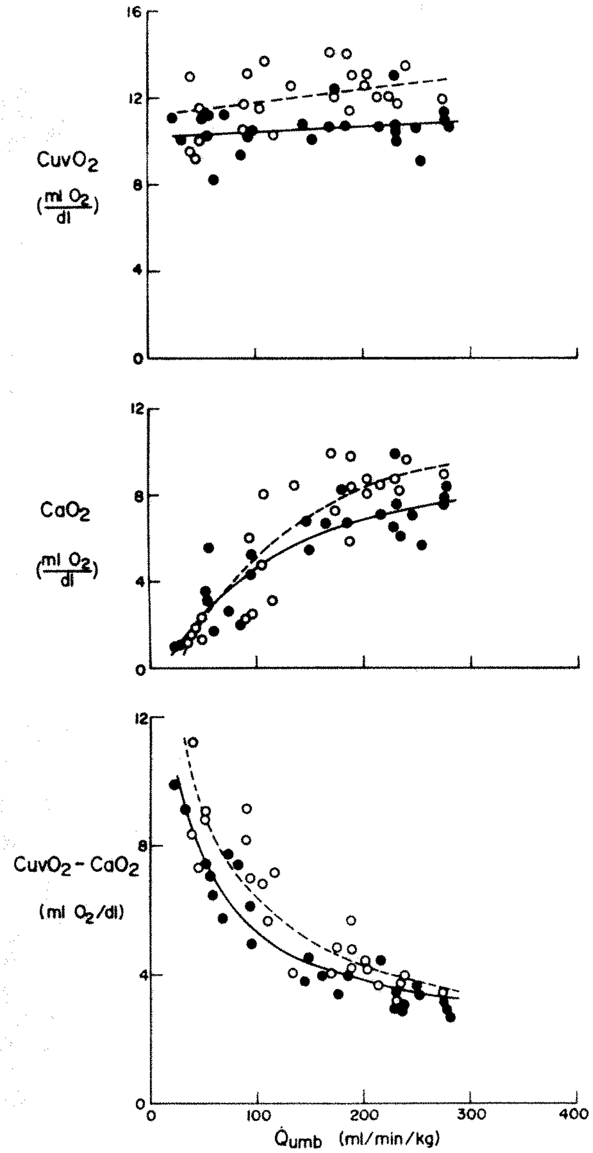

Fig. 1. Relationship of umbilical venous blood oxygen concentration *($CuvO_2$, top)*, fetal femoral arterial blood oxygen concentration *(CaO_2, middle)* and the umbilical venous-arterial oxygen concentration difference *($CuvO_2$-CaO_2, bottom)* to umbilical blood flow *($\dot{Q}_{umb}$)* during maternal oxygen treatment. *Solid circles* ($n = 25$) and *solid regression lines* = room air–treated fetuses; *open circles* ($n = 24$) and *dashed regression lines* = 100% oxygen–treated fetuses. *$CuvO_2$ versus $\dot{Q}_{umb}$:* room air treatment, $y = 10.3 + 0.002x$ ($r = 0.16$, NS); oxygen treatment, $y = 11.0 + 0.008x$ ($r = 0.23$, NS); y intercepts are different ($t = 2.43$, $p < 0.02$). *CaO_2 versus $\dot{Q}_{umb}$:* room air treatment, $y = -8.8 + 2.99 \ln x$ ($r = 0.89$, $p < 0.001$); oxygen treatment, $y = -15.8 + 4.56 \ln x$ ($r = 0.89$, $p < 0.001$); slopes are different ($t = 2.70$, $p < 0.01$). *$CuvO_2 - CaO_2$ versus $\dot{Q}_{umb}$:* room air treatment, $y = 54.2x^{-0.50}$ ($r = 0.96$, $p < 0.001$); oxygen treatment, $y = 76.5x^{-0.55}$ ($r = 0.89$, $p < 0.001$); y intercepts are different ($t = 4.32$, $p < 0.001$).

venous blood Po_2 or Pco_2 significantly (Table I), whereas umbilical venous blood pH decreased at umbilical flows ≤75 ml/min/kg of fetus. In contrast, arterial blood Po_2 decreased while arterial Pco_2 increased during umbilical blood flow reductions. Arterial blood pH fell when umbilical blood flow was reduced to ≤150 ml/min/kg. When compared with room air–treated fetuses, oxygen-treated fetuses had increases in umbilical venous and arterial blood Po_2 values but no significant changes in Pco_2. In oxygen-treated fetuses, arterial blood pH and base excess decreased at umbilical flows ≤75 ml/min/kg.

Fig. 1 and Table II show the effects of maternal oxygen administration on the oxygen concentrations in umbilical venous blood (Cuv_{O_2}) and fetal femoral arterial blood (Ca_{O_2}) and on the umbilical venous-arterial oxygen concentration difference ($Cuv_{O_2} - Ca_{O_2}$). Reductions in umbilical blood flow did not affect Cuv_{O_2} in either room air–treated or oxygen-treated fetuses; Cuv_{O_2} was higher in fetuses whose mothers received 100% oxygen compared with those breathing room air (Fig. 1, *top*). In both treatment groups, Ca_{O_2} decreased with decreasing umbilical blood flow, although Ca_{O_2} was greater in oxygen-treated fetuses than in room air–treated fetuses (Fig. 1, *middle*). Because of these responses, $Cuv_{O_2} - Ca_{O_2}$ increased with decreasing umbilical blood flow in both room air–treated and oxygen-treated fetuses; in oxygen-treated fetuses (when compared with room air–treated fetuses), however, $Cuv_{O_2} - Ca_{O_2}$ was significantly greater at umbilical blood flows ≤150 ml/min/kg (Fig. 1, *bottom*; Table II).

Fig. 2 and Table II illustrate the relationships of fetal oxygen delivery (Do_2) and oxygen consumption ($\dot{V}o_2$) to umbilical blood flow. In room air– and oxygen-treated fetuses, Do_2 was linearly related to umbilical blood flow (Fig. 2, *top*); Do_2, however, was significantly greater in fetuses treated with 100% oxygen (Table II). Because of this greater Do_2, $\dot{V}o_2$ was maintained over a significantly wider range of umbilical flows in oxygen-treated fetuses (75 to 300 ml/min/kg) than in fetuses whose mothers received only room air to breathe (range, 151 to 300 ml/min/kg) (Fig. 2, *bottom*; Table II).

To substantiate that the difference in response of $\dot{V}o_2$ to changes in umbilical blood flow between the two treatment groups was a function of the greater Do_2 available to the oxygen-treated fetuses rather than to other differences in the two groups, we plotted $\dot{V}o_2$ versus Do_2. Fig. 3 shows that the relationship of $\dot{V}o_2$ to Do_2 was the same irrespective of whether fetuses were treated with 100% oxygen or room air, indicating that differences in the $\dot{V}o_2$ response to reduced umbilical flow between the two groups (shown in Fig. 2, *bottom*) were the result of increases in Do_2 in fetuses whose mothers received supplemental oxygen.

Comment

The data presented in this report establish that maternal oxygen administration increases the delivery of oxygen to the fetus during times of reduced umbilical blood flow and that this supplemental oxygen supply

Table II. Effects of maternal oxygen administration on fetal oxygenation during reductions in umbilical blood flow

		Umbilical blood flow ranges (ml/min/kg fetus)			
	Condition	*226-300*	*151-225*	*76-150*	*0-75*
n	RA	9	5	5	6
	O_2	4	8	7	5
$\dot{Q}_{umb}$ (ml/min/kg)	RA	251 ± 21	178 ± 24*	98 ± 29*	49 ± 18*
	O_2	244 ± 21	191 ± 15*	105 ± 18*	45 ± 4*
Cuv_{O_2} (ml O_2/dl)	RA	10.8 ± 1.1	10.9 ± 0.8	10.3 ± 0.6	10.5 ± 1.2
	O_2	12.5 ± 0.9†	12.8 ± 0.9†	12.0 ± 1.2†	10.7 ± 1.6
Ca_{O_2} (ml O_2/dl)	RA	7.6 ± 1.2	6.7 ± 1.1	4.4 ± 1.9*	2.8 ± 1.8*
	O_2	9.0 ± 0.6†	8.4 ± 1.4†	5.0 ± 2.7*	1.8 ± 0.5*
Cuv_{O_2}-Ca_{O_2} (ml O_2/dl)	RA	3.3 ± 0.2	4.2 ± 0.4*	5.9 ± 1.6*	7.7 ± 1.7*
	O_2	3.5 ± 0.4	4.4 ± 0.7*	7.0 ± 1.8*†	8.8 ± 1.5*†
Do_2 (ml O_2/min/kg)	RA	27.4 ± 3.7	19.5 ± 3.1*	10.2 ± 3.4*	5.1 ± 1.9*
	O_2	30.7 ± 3.3†	24.5 ± 1.9*†	12.4 ± 2.7*†	4.8 ± 0.7*
$\dot{V}o_2$ (ml O_2/min/kg)	RA	8.2 ± 0.9	7.5 ± 1.3	5.5 ± 0.5*	3.5 ± 0.8*
	O_2	8.5 ± 0.9	8.5 ± 1.3	7.0 ± 1.1†	4.0 ± 0.6*

n = number of observations; values are means ± SD. RA = Room air; O_2 = 100% oxygen; $\dot{Q}_{umb}$ = umbilical blood flow; Cuv_{O_2} and Ca_{O_2} are umbilical venous and arterial blood oxygen concentrations; Do_2 = fetal oxygen delivery ($\dot{Q}_{umb} \cdot Cuv_{O_2}$); $\dot{V}o_2$ = fetal oxygen consumption ($\dot{Q}_{umb}$ (Cuv_{O_2}-Ca_{O_2})).

*$p < 0.05$ within rows, compared with values obtained in the umbilical flow range of 226 to 300 ml/min/kg.

†$p < 0.05$ within columns, room air measurements versus 100% oxygen measurements.

provides an oxygen reserve with which the fetus can maintain oxidative metabolism. At umbilical blood flows as low as about 75 ml/min/kg of fetus, maternal oxygen administration resulted in increases in the delivery of oxygen to the fetus to a degree sufficient for fetal oxygen consumption to remain stable. In contrast, in fetuses whose mothers received only room air to breathe, oxygen consumption decreased when umbilical blood flow was reduced below about 150 ml/min/kg of fetus.

Oxygen delivery to the fetus is a function of two variables, umbilical blood flow and umbilical venous blood oxygen concentration. In both room air–treated and oxygen-treated fetuses, we found that during reductions in umbilical blood flow fetal oxygen delivery decreased linearly, since umbilical venous blood oxygen concentration was unaffected by reductions in umbilical blood flow.[1,2,5] The fetal compensatory response to this reduction in oxygen delivery was an increase in the extraction of oxygen. The umbilical venous-arterial blood oxygen concentration difference varied as an inverse function of umbilical blood flow and thus of fetal oxygen delivery. As long as fetal oxygen delivery was greater than about 12 ml of oxygen per minute per kilogram of fetus (see Fig. 3), fetal oxidative metabolism was unaffected by this reduction in fetal oxygen supply.[2] When oxygen delivery was ≤12 ml/min/kg, however, fetal oxygen consumption fell along with arterial blood pH and base excess, indicating that the supply of oxygen was inadequate for the demands for oxidative metabolism.[13]

The responses we observed to decreases in umbilical blood flow in room air–treated fetuses were the same as those reported by Itskovitz et al.,[2] even though different methods were used to reduce umbilical blood flow. Itskovitz et al. reduced umbilical blood flow by inflating an occluder located around the umbilical cord. This procedure led primarily to compression of the umbilical vein, increasing umbilical venous blood pressure on the placental side of the obstruction without changing arterial blood pressure. In our experiments, we obstructed the arterial blood supply to the umbilical cord, which decreased arterial blood pressure distal to the obstruction and increased arterial pressure proximal to the obstruction. Despite the differing methods, both studies demonstrated that changes in fetal oxygen delivery and oxygen consumption observed during reductions in umbilical flow were the same even though the effects of these procedures on fetal arterial and venous blood pressures differed (Fig. 4). Taken together, these data therefore support the concept that variations in fetal oxygen delivery have the same effect on fetal oxygen consumption regardless of the specific method used to adversely affect oxygen delivery.[13]

Since oxygen delivery to the fetus is a function of both umbilical blood flow and umbilical venous blood oxygen concentration, a reduction in one variable, for instance, umbilical blood flow as in the present study, may be compensated for by an increase in the other variable, umbilical venous blood oxygen concentration. We undertook the experiments described in this report to determine if oxygen administration to the mother could increase umbilical venous blood oxygen concentration sufficiently to compensate for the reductions in umbilical blood flow that we induced. We found that umbilical venous oxygen concentration could be increased over a wide range of umbilical flows by administering supplemental oxygen to the mother; the um-

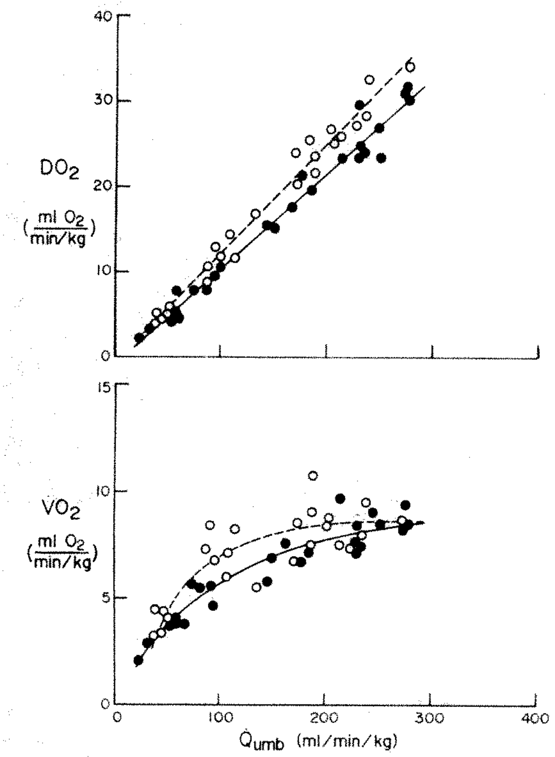

Fig. 2. Fetal oxygen delivery *(DO_2, top)* and fetal oxygen consumption *($\dot{V}O_2$, bottom)* versus umbilical blood flow *($\dot{Q}_{umb}$)* during maternal oxygen treatment. *Solid circles* (n = 25) and *solid regression lines* = room air–treated fetuses; *open circles* (n = 24) and *dashed regression lines* = 100% oxygen–treated fetuses. *DO_2 versus $\dot{Q}_{umb}$:* room air treatment, $y = -0.4 + 0.111x$ ($r = 0.99$, $p < 0.001$); oxygen treatment, $y = -1.1 + 0.132x$ ($r = 0.99$, $p < 0.001$); slopes are different ($t = 3.51$, $p < 0.002$). *$\dot{V}O_2$ versus $\dot{Q}_{umb}$:* room air treatment, $y = -6.6 + 2.68 \ln x$ ($r = 0.94$, $p < 0.001$); oxygen treatment, $y = (-250.3 + 70 \ln x)/\sqrt{x}$ ($r = 0.88$, $p < 0.001$); slopes are different ($t = 4.50$, $p < 0.001$).

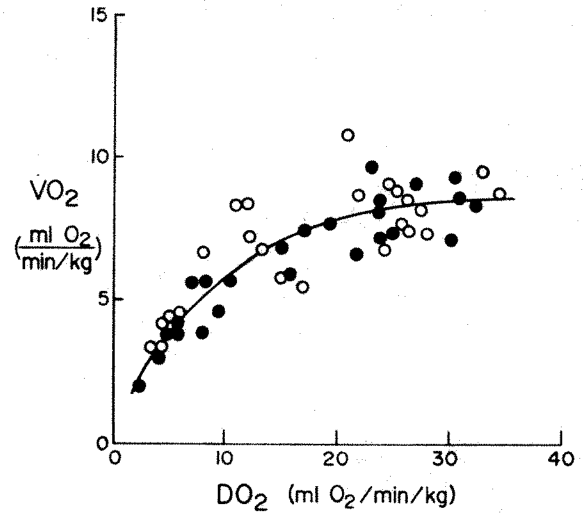

Fig. 3. Relationship of fetal oxygen consumption *($\dot{V}O_2$)* to fetal oxygen delivery *(DO_2)* during maternal oxygen treatment. *Solid circles* (n = 25) = room air–treated fetuses; *open circles* (n = 24) = 100% oxygen–treated fetuses. *$\dot{V}O_2$ versus DO_2:* room air treatment, $y = -0.3 + 2.57 \ln x$ ($r = 0.93$, $p < 0.001$); oxygen treatment, $y = 0.7 + 2.40 \ln x$ ($r = 0.82$, $p < 0.001$); slopes and intercepts do not differ significantly. *Regression line* shown is for combined data (n = 49), $y = 0.1 + 2.51 \ln x$ ($r = 0.87$, $p < 0.001$).

bilical venous blood oxygen concentration was about 15% to 20% greater than the values observed in room air–treated animals. These increases were due to corresponding increases in umbilical venous blood Po_2.[4,6] Since maternal oxygen treatment in the sheep has been shown not to affect uterine or umbilical blood flow or uterine oxygen consumption,[4] the higher umbilical venous Po_2 values were a direct result of increases in the Po_2 and oxygen concentration of maternal arterial and uterine venous blood.[6] In our experiments, when the sheep breathed 100% oxygen, maternal arterial blood Po_2 increased from a mean of 89 mm Hg (hemoglobin 94% saturated with oxygen[14]) to 302 mm Hg (hemoglobin 99% saturated with oxygen), while arterial blood oxygen concentration rose 1.3 ml, from 12.5 to 13.8 ml of oxygen per deciliter of blood. About half of this increase in blood oxygen concentration during maternal oxygen treatment was due to further saturation of hemoglobin with oxygen, while the other half was due to an increase in the quantity of oxygen physically dissolved in plasma. Although we did not measure the uterine venous blood oxygen concentration, this must also have risen about 1.3 ml/dl,[6] since the arterial–uterine venous blood oxygen concentration difference has been shown not to change significantly with oxygen treatment of the pregnant sheep.[4] A rise in uterine venous blood oxygen concentration of about 1.3 ml of oxygen per deciliter would be associated with a rise in uterine venous blood Po_2 of about 10 to 15 mm Hg.[6] Even though such changes in uterine venous blood Po_2 may seem relatively small, they would have led to elevations in umbilical venous blood Po_2 of 10 to 15 mm Hg (and thus to elevations in the umbilical venous blood oxygen concentration of 15% to 20%, as our studies demonstrated), because the sheep placenta functions as a concurrent exchanger for oxygen.[6] With this type of exchanger, uterine venous blood Po_2 exceeds umbilical venous blood Po_2 by a constant amount over a wide range of blood Po_2 values.[6,13]

Maternal oxygen treatment also resulted in increases in fetal arterial blood Po_2 and oxygen concentration over a wide range of umbilical blood flows. In oxygen-treated fetuses, the average arterial blood Po_2 increased up to 6 mm Hg above the values seen in room air–treated animals. Although these increases in arterial Po_2 were relatively small, they were associated with approximately 15% increases in the oxygen concentration of fetal arterial blood. This point is important, because oxygen supply to individual fetal organs is a function of the organ blood flow and the arterial blood oxygen concentration. At any given organ blood flow, oxygen delivery to that organ will be greater when the arterial blood oxygen concentration is greater, as occurs during maternal oxygen treatment. The effects of maternal oxygen treatment on fetal blood oxygen concentrations and Po_2 values that we observed were the same as those reported by Battaglia et al.[4] who studied the effects of oxygen administration to the pregnant sheep on fetal lambs with normal umbilical blood flows. Our observations therefore extend those of Battaglia et al. by demonstrating that, over a wide range of umbilical blood flows, maternal oxygen administration results in increases in the availability of oxygen to the lamb fetus. These increases in oxygen availability enable the fetus to maintain whole-body oxygen consumption over a wider range of umbilical blood flows than the range in fetuses whose mothers receive only room air to breathe.

In view of our findings, we might speculate on the effects of maternal oxygen administration on the adequacy of oxygenation of the human fetus during reductions in umbilical blood flow. Umbilical cord compression, leading to a reduction in umbilical blood flow, occurs commonly during labor. Severe umbilical cord compression can result in fetal distress and asphyxia at birth.[15] If the responses of the human fetus to reductions in umbilical blood flow are the same as those we have observed for the lamb fetus, then compression of the umbilical cord would cause a reduction in fetal oxygen delivery, which could adversely affect fetal oxidative metabolism. Furthermore, if the responses of the human fetus to maternal oxygen administration during reductions in umbilical blood flow are similar to those we have observed for the lamb fetus, then administration of supplemental oxygen to the mother should enhance the fetus' ability to maintain aerobic metabolism despite the reduced umbilical flow. Maternal oxygen administration may, therefore, be a clinically useful treatment, in combination with other clinically accepted maneuvers such as changes in maternal position, in instances of fetal distress due to umbilical cord compression during labor. There are, however, likely to be quantitative differences between the responses of sheep and human fetuses to oxygen treatment, because sheep, which have slightly lower hemoglobin-oxygen saturations than do women breathing room air,[14] might benefit more when supplemental oxygen is administered.

In summary, we have demonstrated that oxygen administration to the pregnant sheep increases the delivery of oxygen to the fetus during episodes of reduced umbilical blood flow. The fetal lamb can use this supplemental oxygen delivery to maintain oxidative metabolism despite substantial reductions in its umbilical perfusion. These data may be relevant to those clinical conditions characterized by reductions in umbilical blood flow.

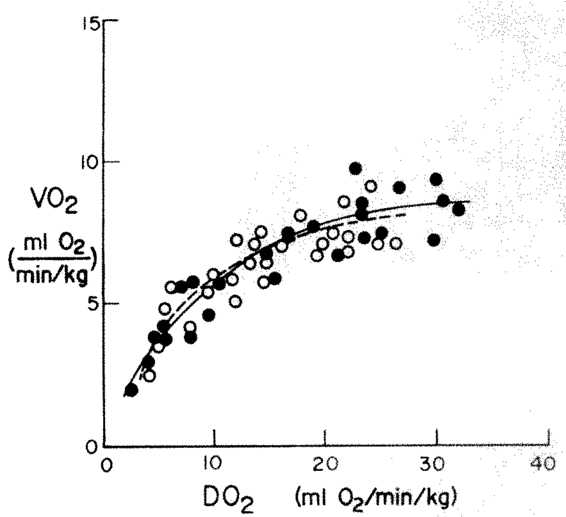

Fig. 4. Comparison of data relating fetal oxygen consumption *($\dot{V}O_2$)* to fetal oxygen delivery *(DO_2)* during reductions in umbilical blood flow, taken from two studies using different methods for reducing umbilical blood flow. *Solid circles* (n = 25) and *solid regression line* = reductions due to obstruction of umbilical arterial blood flow (data from present study, room air treatment only); *open circles* (n = 26) and *dashed regression line* = reductions due to obstruction of umbilical venous blood flow (data from Itskovitz et al.[2]). *$\dot{V}O_2$ versus DO_2:* present study, room air treatment only, $y = -0.3 + 2.57 \ln x$ ($r = 0.93$, $p < 0.001$); *$\dot{V}O_2$ versus DO_2:* data from Itskovitz et al.,[2] $y = -23.92\ (1/x) + 8.38$ ($r = 0.87$, $p < 0.001$).

We wish to thank Anthony Battelli, Patrick Moran, and Betty Steranka for their skillful technical assistance.

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CORRESPONDENCE

Ultrasound diagnosis of meconium-stained amniotic fluid

To the Editors:

We read with interest the report by Benacerraf et al. entitled "Ultrasound diagnosis of meconium-stained amniotic fluid" (AM J OBSTET GYNECOL 1984;149:570).

Technically we are surprised that the authors did not mention the traditional method of detecting meconium in amniotic fluid using transcervical amnioscopy as advocated by Saling.[1] This noninvasive technique is a standard practice for the management of postdate and high-risk pregnancies in many centers. An advantage of this procedure is that, whenever meconium is detected, amniotomy under direct vision to confirm the finding can be considered and has been shown to be easy and safe.[2]

In your report the presence of meconium in the amniotic fluid was confirmed 1 to 4 days after ultrasonic diagnosis. The meconium could have been passed after the ultrasound examination. The authors' findings would have been more convincing if amniotomy, amnioscopy, or amniocentesis was carried out immediately after scanning to confirm their findings.

We agree with the authors that the presence of meconium in the amniotic fluid at the time the membranes rupture or during early labor is associated with fetal distress. If the membranes are ruptured, no ultrasound scanning would be necessary. If meconium is suspected in early labor before the membranes are ruptured, we feel that amniotomy would be a better diagnostic and management procedure.

There remain cases where the fetus may pass meconium before the onset of labor. The significance of this is still uncertain, since the fetus may pass and subsequently reabsorb meconium when there is no obstetric complication. The use of ultrasound diagnosis of meconium, even if valid, will lead to an excess of false positive diagnosis of fetal distress.

We feel that a careful clinical evaluation of the pregnancy and the use of more standard fetal welfare tests remain the best management for high-risk pregnancies. If there is a need to detect meconium in the amniotic fluid near term, amnioscopy is a noninvasive and time-tested procedure.

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Reply

To the Editors:

We are grateful for the interest of Drs. Wong, Long, and Chang in our paper, "Ultrasound diagnosis of meconium-stained amniotic fluid." The purpose of our report was to describe a novel method of identifying the presence of meconium-stained amniotic fluid ante partum. We did not mention the method of detecting meconium by means of transcervical amnioscopy, since it is not at present in use in our institution or area and had not been used in the past. Furthermore, I do not believe that it represents a "traditional" method for the detection of meconium-stained amniotic fluid in this country. It is also an invasive technique, which requires instrumentation of the cervix, and in this way cannot be compared to a sonogram.

We agree that when the membranes are ruptured, no ultrasound scanning is necessary to detect meconium, and we did not address the situation when meconium may be suspected in early labor. Our report simply describes the appearance of meconium-stained fluid ante partum, and immediate confirmation of our finding was not possible, because neither amniocentesis, amnioscopy, or amniotomy was indicated at the time.

We agree that the presence of meconium-stained amniotic fluid during labor is associated with fetal distress. Prior to our sonographic findings, a noninvasive method of detecting meconium ante partum was not available. As stressed in the discussion of our paper, the correlation of this finding with fetal distress has therefore not been established and more work is needed to determine whether this sonographic finding should alter clinical management.

In conclusion, we feel that new methods of fetal testing, particularly noninvasive ones, should be welcomed and may in time replace the older ones.

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Natural killer cell activity during pregnancy

To the Editors:

I have read with great interest the paper by Okamura et al. (AM J OBSTET GYNECOL 149:396, 1984) in which they report a depressed maternal natural killer cell activity during pregnancy.

An interesting fact reported by them was that natural killer cell activity in pregnant women exhibited a negative correlation to the birth weight of the baby.

They mentioned in their comment that this negative correlation may suggest that a natural killer cell attack on the trophoblast would damage the functions of the placenta in spite of its normal appearance, but they did

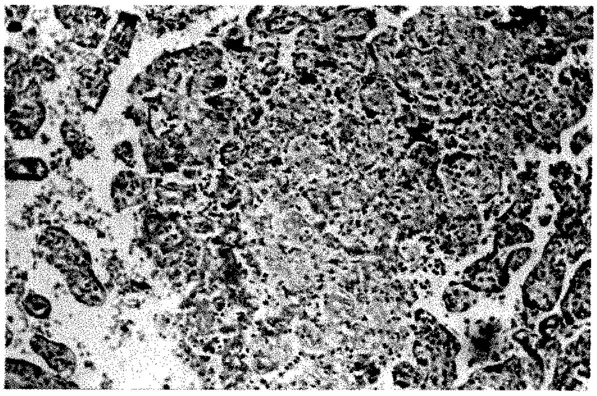

Fig. 1. Chorionic villi with fibrinoid necrosis, stromal lymphocytic infiltration, and trophoblastic necrosis (chronic villitis). (Hematoxylin-eosin stain. × 100.)

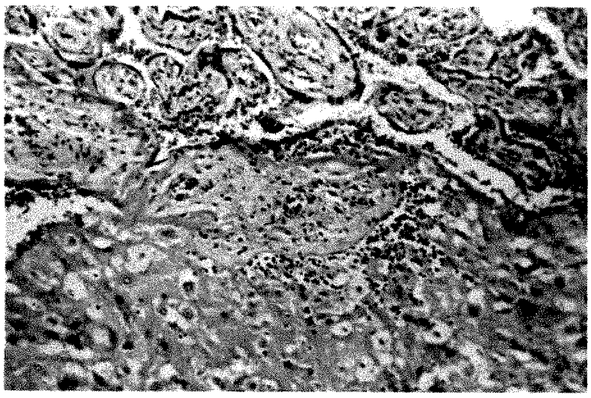

Fig. 2. Anchoring villus surrounded and infiltrated by lymphocytes (anchoring villitis). (Hematoxylin-eosin stain. × 100.)

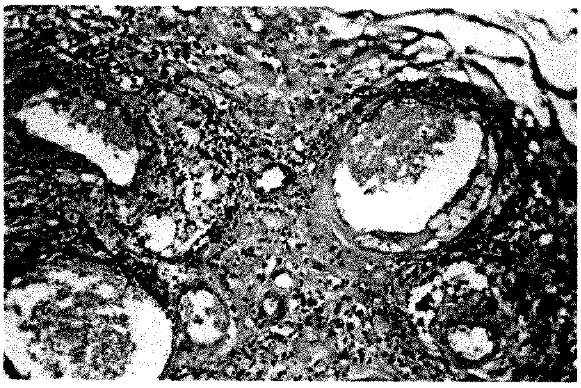

Fig. 3. Vessel of the basal decidua with fibrinoid necrosis of the wall and lipid-laden macrophages, surrounded by a rim of lymphocytes (acute atherosis). (Hematoxylin-eosin stain. × 100.)

not mention anything about the histopathologic findings for these placentas.

We have recently described[1-5] lesions of chronic villitis (Fig. 1), anchoring villitis (Fig. 2), and acute atherosis (Fig. 3) associated to the absence of trophoblastic invasion in spiral arteries in placentas of term idiopathic small–for–gestational age infants. These placental lesions were significantly higher in placentas from small–for–gestational age infants than in those from infants with normal birth weight, and a negative correlation to the birth weight of the infant was observed.

A defect of blocking factors (enhancing antibodies) associated with a maternal immune attack mediated by the T cell subpopulation of lymphocytes with cytotoxic damage to placental and fetal tissues has been proposed as the cause for these lesions.[1]

Likewise, an attack by natural killer cells on the trophoblast or another natural resistance should take place probably prior to the immune attacks by cytotoxic T lymphocytes and be associated with the above-mentioned placental lesions.

I would like to know whether the authors have found a higher natural killer cell activity in mothers with term idiopathic small–for–gestational age infants and whether the placentas from these cases showed any histopathologic lesion.

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Reply

To the Editors:

I would like to thank Dr. Labarrere for his comment on our article.

In regard to his question, unfortunately no histologic samples were obtained from the placentas of the mothers whose natural killer activities were high, because the main purpose of our work at the time was to find an immunologic indicator to predict the clinical course of pregnancy. Therefore this information is not available.

As he mentioned, it is quite important to examine placenta histologically. Looking at his pictures, I am interested in what types of mononuclear cells, including natural killer cells, appear in the lesions.

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Sonographic appearance of the ovarian thecoma

To the Editors:

In a recent report (Diakoumakis E, Vieux U, Seife, B. Sonographic demonstration of thecoma: report of two cases. AM J OBSTET GYNECOL 1984;150:787), Diakoumakis et al. emphasized the uniqueness of the sonographic appearance of the ovarian thecoma, that of a mass without calcification which cast a dense accoustic shadow. The same appearance was described previously in another report.[1] The lack of echogenicity within the tumor is most likely the result of the marked homogeneity of the substance within it, which created no interface to the ultrasonic beam. At the same time the dense fibrous components of this tumor impede ultrasonic transmission to give rise to the shadowing that is thought to be characteristic of this tumor.

We recently came across a case of thecoma in a 26-year-old woman who came to the ultrasound room because of a palpable hard mass in the lower abdomen. An oval-shaped echolucent mass measuring 8 by 11 by 7 cm with a crescentic band of low-level echoes in the superior aspect of the mass was observed. The posterior margin of the mass was well defined, and acoustic shadowing was not apparent behind the mass (Fig. 1). At laparotomy a solid ovarian tumor of the same size was removed. Histologic examination revealed dense regular spindle-shaped cells arranged in whorls consistent with the diagnosis of ovarian thecoma.

The sonographic appearance of this tumor was not characteristic of what has been described except that the greater part of the tumor gave a "cystic" appearance. Although the typical sonographic findings in a thecoma can be explained on theoretical grounds, dense acoustic shadowing does not appear to be pathognomonic of this ovarian tumor. The size of the tumor reported here is smaller than that reported by Diakoumakis et al. and by Yaghoobian and Pinck,[1] so it is possible that acoustic shadowing will eventually become apparent when the mass grows to a larger size. The other explanation of the difference in sonographic characteristics reported here is the heterogeneity in the composition and consistency which may occur in these tumors.[2]

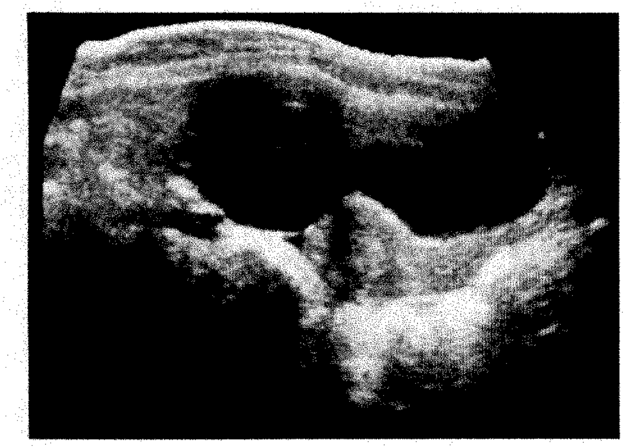

Fig. 1. Longitudinal scan 2 cm to the right of midline. An oval-shaped echolucent mass is seen above the fundus of the uterus with a crescentic band of low-level echoes seen at the superior aspect of the mass. The posterior margin of the mass is well defined, and dense acoustic shadowing is not present.

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Hormone levels and premenstrual syndrome

To the Editors:

The paper entitled "Premenstrual syndrome: weight, abdominal swelling, and perceived body image" by Dr. Faratian et al. (AM J OBSTET GYNECOL 1984;150:200-204) contained some interesting ideas and methods of assessment. However, they draw conclusions which cannot be substantiated because of insufficient data and should therefore not have been made.

In their comments they state that the measurement of ovarian hormones proved to be of no value in distinguishing between groups of patients. They also conclude that their findings showing no significant differences between estrogen and progesterone levels and their ratio between the groups lead them to suspect that premenstrual syndrome patients do not have low progesterone levels or changed progesterone/estrogen ratios. These statements cannot be made on the limited hormonal data available, as was discussed with the authors when the medical report of the study was prepared in collaboration with them. The number of patients in each group was small and each patient only had one blood sample taken for hormone assay during the premenstrual period and another during the preovulatory period. It was obviously impossible to time the taking of these single samples precisely in relationship to ovulation and menstruation, and therefore the variables are enormous and thus present no opportunity to draw comparisons.

As the authors state, much has been written to suggest that premenstrual syndrome is due to a relative deficiency of progesterone in the luteal phase of the cycle,[1,2] a relative increase in estradiol,[3] or a change in the progesterone/estradiol ratio.[4] These conclusions have been drawn from studies in which more frequent hormone assays have been carried out during the menstrual cycle. However, in order to try and confirm any of these postulated causes of premenstrual syndrome or make alternative statements, it is necessary to look at daily (or more frequent) samples in both the follicular and luteal phases. The use of saliva samples now makes this possible, and we hope to be reporting results in due course.

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Reply

To the Editors:

Dr. Martin appears to have misunderstood the small section of our paper in which we concluded that single measurements of estrogen and progesterone were of no value in distinguishing between symptomatic women and controls and hence of no use in diagnosis. He suggests that we attempt to refute the theory of progesterone deficiency on the basis of a limited number of blood samples. This we have not done, did not intend to do, and would not expect to do. It is clear that if differences are to be shown in ovarian steroid levels in premenstrual syndrome, frequent sampling would be required. However, in our discussion, we did cite data from previous studies which showed how confused our knowledge is in this respect. It is possible to find results of research studies to support excess progesterone,[1] deficiency of progesterone,[2] or more recently, no differences in progesterone.[3] Dr. Martin has chosen to relate only those studies from 8 and 10 years ago which support a progesterone-deficiency hypothesis. (These studies contain a smaller number of patients than in our paper, which is surprising because he concluded that our study of 148 menstrual cycles was too few.) It is important to point out that we do not support a theory of either deficiency or excess of progesterone and would like to reiterate that the purpose of ovarian hormone measurement in our study was not to determine the etiology of premenstrual syndrome but to evaluate the ability to diagnose premenstrual syndrome from a single blood sample. That it proved to have no value in distinguishing these patients from controls is not surprising in view of the conflicting data in the literature.

These arguments concerning the progesterone should not be allowed to cloud the main issue of the study suggesting that severe symptoms of bloatedness and an increase in perceived body image can occur in the absence of actual changes in body dimensions. In addition, bloatedness and over-estimation of perceived body size appear to occur in the absence of weight increase and therefore, by inference, in the absence of water retention.

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Sinusoidal fetal heart rate and butorphanol administration

To the Editors:

Just before the publication of "Sinusoidal fetal heart rate patterns associated with intravenous butorphanol administration: a case report" (Engel JL, Knuppel RA, Lake M. AM J OBSTET GYNECOL 1984;149:465), a similar instance occurred in our institution. Intravenous and intramuscular butorphanol (Stadol) is frequently administered in active-phase labor on our university service; 1 mg intravenously and 1 mg intramuscularly are administered.

In the last 188 cases in which this form of analgesia was given to active labor patients, we have noted two instances in which there is a significant temporal relationship between the administration of butorphanol and the onset of a sinusoidal fetal heart rate pattern. Patterns have consisted of regular oscillations with an amplitude of 15 bpm in a normal heart range of 120 to 160 bpm. The frequency was between 3 and 5 cycles per minute with considerable difficulty in determining short-term variability. In both instances the sinusoidal pattern dissipated at about the same time the patient requested pain relief again prior to complete dilatation. In both instances (one normal spontaneous vaginal delivery and one cesarean section for secondary arrest of dilatation and descent), the infants were born with Apgar scores of ≥8 at 1 minute and ≥9 at 5 minutes. Both infants were appropriately grown term infants with hematocrits in the range of 60 to 65. In both cases neonatal heart rate, neonatal examination, and nursery course for the baby were totally uncomplicated, and the infants were discharged home with the mother.

Over the past 9 months butorphanol has been used with great success for analgesia during active labor, with only these two instances of significant change in the fetal heart rate pattern. As indicated by Engel et al., the presence of this pattern in temporal relationship with the administration of butorphanol appears to have elicited this sinusoidal fetal heart rate pattern in the fetus. In our series an incidence of just over 2% was noted. This in no way diminishes the potentially ominous significance of this pattern as previously reported by Modanlou and Freeman.[1] However, it does emphasize the conclusion of Engel et al. that further evaluation of the fetus will be necessary in the presence of alphaprodine (Nisentil) and butorphanol.

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Cesarean section delivery and future childbearing

To the Editors:

The study by Zdeb et al. (Frequency, spacing, and outcome of pregnancies subsequent to primary cesarean childbirth. AM J OBSTET GYNECOL 1984;150:205) showing a decrease in future pregnancies among patients who undergo primary cesarean section probably comes as a surprise only to those who themselves have never undergone a major surgical procedure.

While the pain of labor often fades and dims in a patient's mind, the prolonged pain and discomfort associated with abdominal surgery do not. What may seem to a physician a relatively simple 1-hour operation inflicts considerable anguish and suffering upon one on whom it is performed.

For some women who have greeted their infants in a surgical atmosphere, childbirth represents a maze of anxiety, anesthesia, intravenous equipment, pain, Demerol, nausea, and frequent depression. The tremendous physical and psychological burden exacted by surgical childbirth is an anathema, as is the prospect of again attempting to care for a helpless newborn infant while recovering from major surgery. Is it so remarkable that these patients have no desire to undergo a repeated major abdominal operation with its attendant risks for themselves and their infants? Would you?

As physicians well know, for a few unfortunate women the morbidity associated with cesarean section permanently ends their reproductive ability. Perhaps for a greater number, however, once a cesarean—is enough.

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Columbus, Georgia 31904

Genital chlamydial infection and cervical cancer

To the Editors:

We read with great interest the series of articles by Reid et al., published in this journal (AM J OBSTET GYNECOL 1984;149:293, 149:815, and 150:189) and other journals,[1-3] on genital warts and cervical cancer. We would like to make the following comments, since we are involved presently with an ongoing investigation of the possible association between genital chlamydial infection and cervical cancer.

Chlamydia trachomatis has been recognized as one of the most common of the sexually transmitted agents, and several recent studies suggest also an association between cervical chlamydial infection and cervical neoplasia: *C. trachomatis* was isolated significantly more frequently from cervices of women with cervical intraepithelial neoplasia and invasive cervical cancer than from cervices of control subjects.[4-7] Cervical cellular atypia and dysplasia were noted more frequently in women with chlamydial cervicitis[8, 9] than without the disease and in women who were seropositive than in women who were seronegative for antibodies to *C. trachomatis.*[10] A correlation was found between chlamydial cervical infection and lymphoid follicle formation (follicular cervicitis).[9] Follicular cervicitis was found in 35% of cervices that showed evidence of cervical intraepithelial neoplasia whereas no follicular cervicitis was found in any of the cervices that showed no evidence of cervical intraepithelial neoplasia.[6] In cervical secretions, local IgA antibodies to *C. trachomatis* were found in 100% of patients with invasive cervical cancer, 61% of patients with cervical intraepithelial neoplasia, 39% of patients with cervicitis, and 12% of control subjects.[11] It is significant that higher serum antibody titers to *C. trachomatis* were found in women with cervical neoplasia than in control subjects.[4, 5] A stronger association with cervical neoplasia for serum chlamydial antibodies than for herpes simplex virus 2 antibodies was found.[5, 7]

Thus we suggest that the possibility of a coexistent cervical chlamydial infection with any of the other sexually transmitted agents should be taken into consideration and that future studies of cervical neoplasia should also control for chlamydial infection. This is particularly important, since there is an effective and specific treatment for chlamydial infection (that is, doxycycline hydrochloride), and early treatment may prevent the development of cervical neoplasia in some women.

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Reply

To the Editors:

Piura et al. are correct in pointing to an association between cervical neoplasia and *Chlamydia trachomatis* infection. However, since the prevalence of both entities reflect life-style and sexual habits, one must be very cautious about interpreting such a relationship as having etiologic significance. Admittedly, linear logistic analysis suggests that this association persists after matching for markers of sexual activity. However, an odds ratio of 2 : 1 is well within the realm of a spurious correlation. *Chlamydia trachomatis* is not known to be oncogenic, does not induce neoplastic transformation of mammalian cell cultures, and is not implicated in the etiology of any animal malignancies. Moreover, there is no clear-cut morphologic spectrum linking chlamydial cervicitis to intraepithelial neoplasia. In short, there is little supporting evidence to give plausibility to the suggestion that this may be a causal association.

Most papillomaviral-induced malignancies appear dependent upon the operation of various cofactors. Certainly the epidemiologic discrepancies between the prevalence of benign warty infection and that of cervical cancer suggest that unidentified cocarcinogens may play an important role in the pathogenesis of squamous carcinoma in the lower genital tract. Whether as a measure of cocarcinogenic potential or simply as a means of standardizing the sexual life-styles of the subjects, future analyses of the relationship between papillomaviral infection and cervical neoplasia should, wherever possible, attempt to define the prevalence of coexistent chlamydial infection in both study and control groups.

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IN MEMORIAM

Howard C. Taylor, Jr., M.D.

1900-1985

The Editors and The C. V. Mosby Company, Publisher of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, pay tribute to Dr. Taylor, a man of great stature in the United States and the world in the fields of obstetrics and gynecology, cancer, planned parenthood, and education and in the field of medical publication as Editor in Chief of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. He accomplished many superb things in our specialty and left his imprint on every task he undertook. He will always be remembered for his initiative, insight, energy, wisdom, and editorial abilities.

He served as an Associate Editor of the JOURNAL from 1936 to 1953, then as Co-Editor with Dr. William J. Dieckmann until 1958. In 1959 he became Editor in Chief, and served with distinction until 1969, when he became Emeritus Editor.

Being interested in education and believing the JOURNAL was an ideal method for the broad dissemination of information, Dr. Taylor began an effort to attract foreign authors to submit their manuscripts to the JOURNAL. He was suited to this endeavor because of his excellent international reputation and activities. It was a success. The number of worthy manuscripts increased and the number of foreign readers increased.

As a result of the rapid expansion of clinical investigation and basic research in the field of obstetrics and gynecology, a larger number of manuscripts suitable for publication were submitted to the JOURNAL. Dr. Taylor acted promptly and the publication of the JOURNAL was changed in 1962 from 12 issues a year to 24 issues a year with full support of the Publisher.

Along with these changes Dr. Taylor brought the JOURNAL to a full and complete peer review status, which improved its quality.

His organizational ability and leadership were apparent throughout the 34 years he served the JOURNAL in an editorial capacity and in the years he was Emeritus Editor.

Dr. Taylor graduated from the College of Physicians and Surgeons, Columbia University, New York City, in 1924, became Professor and Chairman, Department of Obstetrics and Gynecology, New York University College of Medicine in 1943, and then in 1946 was appointed Professor and Chairman of the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and served in exemplary fashion until his retirement in 1965.

Dr. Taylor was extremely active in organized medicine and has served as president of the following organizations: American College of Obstetricians and Gynecologists, 1965; American Gynecological Society, 1958; International Federation of Gynecology and Obstetrics, 1961; American Cancer Society, Inc., 1955; American Association of Planned Parenthood Physicians, 1966; New York Obstetrical Society, 1950; and New York Gynecological Society, 1962. He was a member of 22 societies in the United States.

Howard was honored by many foreign countries. He was an Honorary Fellow of the Royal College of Obstetrics and Gynaecology, Edinburgh Obstetrical Society, Deutsche Gesellschaft für Gynäkologie, The Japanese Obstetrical and Gynecological Society, Societa Italiana di Ostetricia e Ginecologia, Societe Française de Gynecologie, Society Brasileira de Ginecologia, Sociedad Peruana de Obstetricia y Ginecologia, Association of Gynecologists and Obstetricians of Yugoslavia, Sociedade de Ginecologia e Obstetricia de Pernambuco, and the Czechoslovak Medical Society.

In addition to these accomplishments, Dr. Taylor conducted educational and training programs for residents and fellows, which produced outstanding academic and clinical obstetricians and gynecologists, and at the same time published approximately 180 articles of his own scientific studies.

It has been a privilege for the Editors and all the personnel at The C. V. Mosby Company to work with Dr. Taylor, a scholar, scientist, educator, and gentleman. His imprint on the JOURNAL will always remain. We also express our gratitude to his wife, Caroline Colgate Taylor, for her support of him in his editorial commitments and for her time and effort devoted to him in his full life. We shall miss him.

Books received

Atlas of Obstetric, Gynecologic, and Perinatal Ultrasonography. Edited by Kenneth J. W. Taylor. 433 pages, illustrated. New York, 1984, Churchill Livingstone, Inc. $50.00.

Chronic Ulcers of the Skin. Bok Y. Lee. 224 pages, illustrated. New York, 1985, McGraw-Hill Book Company. $27.00.

Gray's Anatomy of the Human Body. Thirtieth American Edition. Edited by Carmine D. Clemente. 1676 pages, illustrated. Philadelphia, 1985, Lea & Febiger. $68.50.

Human Trophoblast Neoplasms. Edited by Roland A. Pattillo and Robert O. Hussa. 504 pages, illustrated. New York, 1984, Plenum Press. $72.50.

Laser Surgery in Gynecology and Obstetrics. William R. Keye. 196 pages, illustrated. Boston, 1985, G. K. Hall Medical Publishers. $35.00.

Pathology of the Placenta. Edited by Eugene V. D. K. Perrin. 225 pages, illustrated. New York, 1984, Churchill Livingstone, Inc. $45.00.

Perspectives on Abortion. Edited by Paul Sachdev. 279 pages. Metuchen, New Jersey, 1985, The Scarecrow Press, Inc. No price listed.

The Principles and Practice of Ultrasonography in Obstetrics and Gynecology. Third Edition. Edited by Roger C. Sanders and A. Everette James. 663 pages, illustrated. Norwalk, Connecticut, 1985, Appleton-Century-Crofts. No price listed.

Pulmonary Surfactant. Edited by Bengt Robertson, Lambert M. G. Van Golde, and Joseph J. Batenburg. 582 pages, illustrated. New York, 1984, Elsevier Science Publishers. $134.50.

Respiratory Distress Syndrome. Edited by Kari O. Raivio, Niilo Hallman, Kauko Kouvalainen, and Ilkka Välimäki. 421 pages, illustrated. Orlando, Florida, 1984, Academic Press, Inc. $55.00.

The At-Risk Infant. Psycho/Socio/Medical Aspects. Edited by Shaul Harel and Nicholas J. Anastasiow. 428 pages. Baltimore, Maryland, 1984, Paul H. Brookes Publishing Co. $44.95.

ITEMS

Announcements of major meetings and other significant activities must be received at least 8 weeks before the desired month of publication. All announcements carry a charge of $45.00 U.S. and the fee must accompany the request to publish. Information will be limited to title of meeting, date, place, and an address to obtain further information. Send announcements and payment, payable to this JOURNAL, to The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63146.

Teratology—Principles and Clinical Applications, July 27–August 1, 1985, Snowmass, Colorado. For further information contact: Lee Pickles, CME, Scott & White, Temple, TX 76508. Tel.: (817) 774-4083.

The Mt. Sinai Medical Center of Cleveland Fifth Annual Workshop in Fertility Microsurgery Including In Vitro Fertilization, The Mt. Sinai Medical Center, Cleveland, Ohio. Basic Course: September 9-11, 1985. Advanced Course: September 12-14, 1985. For further information contact: Dr. James M. Goldfarb, The Mt. Sinai Medical Center, University Circle, Cleveland, OH 44106.

London and Paris Fall Ultrasound—Obstetrics and Gynecology, London, England, September 20-25, 1985; Paris, France, September 25-29, 1985. For further information contact: Secretary, Fall Ultrasound Symposia, Medical Seminars International, West Park Medical Office Building, 22135 Roscoe Blvd., #104, Canoga Park, CA 91304. Tel.: (818) 340-0580, ext. 280.

A Clinical and Histopathologic Overview of Obstetrics and Gynecology, September 24-28, 1985, New York Hilton, New York, New York. For further information contact: Department of Obstetrics and Gynecology, Saint Barnabas Medical Center, Livingston, NJ 07039.

Birth Defects Symposium XVI, Genetic Disease Screening and Management, September 30–October 1, 1985, Albany Hilton Hotel, Albany, New York. For further information contact: Thomas P. Carter, Ph.D., Wadsworth Center for Labs and Research, Rockefeller Empire State Plaza, Albany, NY 12201.

Specialty Review in Obstetrics and Gynecology, October 28–November 2, 1985, Chicago, Illinois. For further information contact: Dick Nelson, Course Manager, The Cook County Graduate School of Medicine, 707 South Wood St., Chicago, IL 60612. Tel.: (312) 633-2600.

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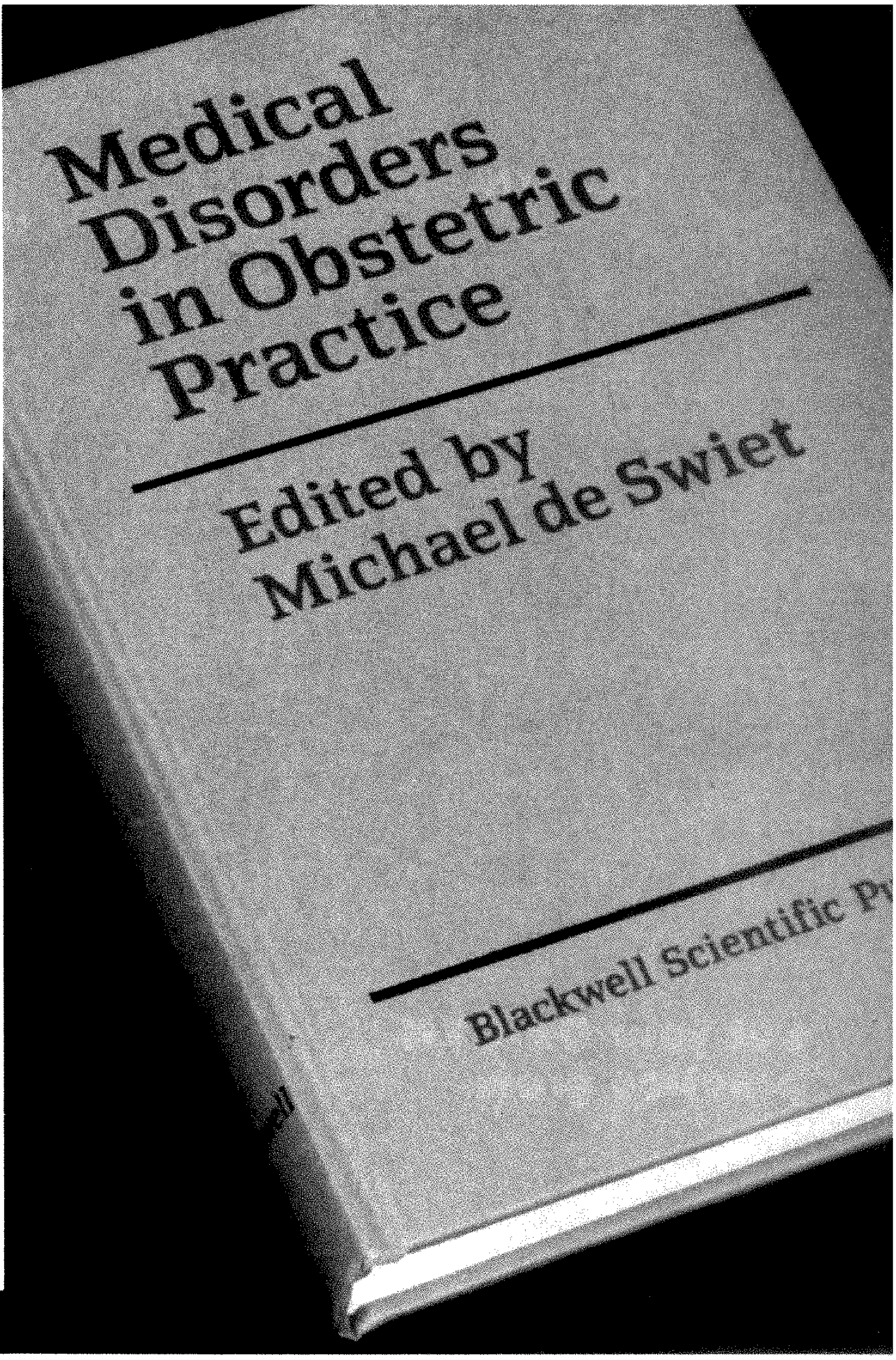
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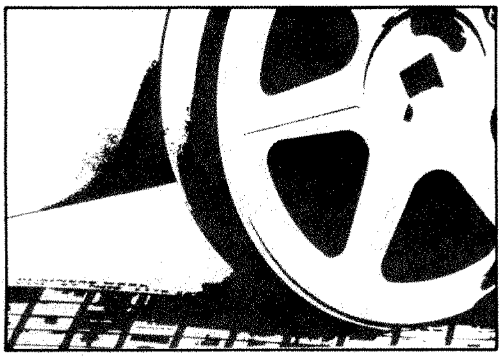

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WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke. The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1 THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established Four principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause Overall excess mortality due to pulmonary embolism or stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age **CEREBROVASCULAR DISORDERS:** In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than in nonusers. A prospective study conducted in Great Britain estimated that former users have a risk for all cerebrovascular disease 2.6 times greater than that of nonusers This risk remained elevated for at least six years after last oral contraceptive use. A prospective study conducted in the United States found that past use of oral contraceptives was associated with increased risk of subarachnoid hemorrhage the relative risk being 5.3 There was also some evidence from this study that the degree of risk may be related to duration of oral contraceptive use **MYOCARDIAL INFARCTION:** An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported confirming a previously suspected association These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30-39 age group and 67 cases per 100,000 women users in the 40-44 age group In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke Oral contraceptive users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent. A study suggests that some increased risk of myocardial infarction in oral contraceptive users persists following discontinuation of oral contraceptives and that the degree of the residual risk is related to the duration of the past use. **Risk of Dose:** In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only oral contraceptives have not been performed Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age Oral contraceptives are, however, an independent risk factor for these events. **ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES:** A large prospective study carried out in the United Kingdom estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000, ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous versus intermittent use Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group This study reports that the increased risk of circulatory disease mortality may persist after the pill is discontinued Another study published at the same time confirms a previously reported increase of mortality in pill users from cardiovascular disease The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke (The rates given for pill only/smokers for each age group are for smokers as a class For "heavy" smokers [more than 15 cigarettes a day], the rates given would be about double, for "light" smokers [less than 15 cigarettes a day], about 50 percent.) The mortality associated with oral contraceptive use in nonsmokers over 40 is higher than with any other method of contraception in that age group The lowest mortality is associated with the condom or diaphragm backed up by early abortion The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis) Should any of these occur or be suspected, the drug should be discontinued immediately A four- to six-fold increased risk of postsurgery thromboembolic complications has been reported in oral contraceptive users If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization 2 OCULAR LESIONS There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures 3 CARCINOMA Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on oral contraceptives Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occurred in women who had used a sequential oral contraceptive These products are no longer marketed No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives. Several studies have found no increases in breast cancer in women taking oral contraceptives or estrogens One study, however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of oral contraceptives has been well-documented In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception 4 HEPATIC TUMORS Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study showed that oral contraceptive formulations with high hormonal potency were associated with a higher risk than lower potency formulations and use of oral contraceptives with high hormonal potency and age over 30 years may further increase the woman's risk of hepatocellular adenoma. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage This has been reported in short-term as well as long-term users of oral contraceptives Two studies relate risk with duration of use of the contraceptive, the risk being much greater after four or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives The relationship of these drugs to this type of malignancy is not known at this time 5. USE IN OR IMMEDIATELY PRECEDING PREGNANCY, BIRTH DEFECTS IN OFFSPRING, AND MALIGNANCY IN FEMALE OFFSPRING The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare This risk has been estimated to be on the order of 1 to 4 in 1000 exposures. Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy Male children so exposed may develop abnormalities of the urogenital tract Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy. One case control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives Embryos with these anomalies are virtually always aborted spontaneously Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if the progestogen-only oral contraceptives are used), and further use of oral contraceptives should be withheld until pregnancy has been ruled out If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive Many clinicians recommend three months although no precise information is available on which to base this recommendation The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy 6. GALLBLADDER DISEASE. Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and estrogens In one study, an increased risk appeared after two years of use and doubled after four or five years of use. In one of the other studies, an increased risk was apparent between six and twelve months of use. 7 CARBOHYDRATE AND LIPID METABOLIC EFFECTS. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives. The clinical significance of this finding remains to be defined 8 ELEVATED BLOOD PRESSURE An increase in blood pressure has been reported in patients receiving oral contraceptives In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug 9 HEADACHE The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause 10. BLEEDING IRREGULARITIES Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods Postuse anovulation, possibly prolonged, may also occur in women without previous irregularities. 11 ECTOPIC PREGNANCY Ectopic as well as intrauterine pregnancy may occur in contraceptive failures 12. BREAST FEEDING Oral contraceptives given in the postpartum period may interfere with lactation There may be a decrease in the quantity and quality of the breast milk Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs The effects, if any, on the breast-fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned **PRECAUTIONS: General:** 1. A complete medical and family history should be taken prior to the initiation of oral contraceptives The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed 2 Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3 Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related 4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution and only with careful monitoring in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency 5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy If jaundice develops in any patient receiving such drugs, the medication should be discontinued 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients 7 Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency The clinical significance of this is yet to be determined 8 Serum folate levels may be depressed by oral contraceptive therapy Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency 9 The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted 10 Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a Increased sulfobromophthalein retention b Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability c Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered d Decreased pregnanediol excretion e Reduced response to metyrapone test **INFORMATION FOR THE PATIENT: (See Patient Package Insert). DRUG INTERACTIONS:** Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin, griseofulvin, and tetracycline. **CARCINOGENESIS, PREGNANCY, NURSING MOTHERS: See CONTRAINDICATIONS and WARNINGS. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS). Thrombophlebitis Pulmonary embolism Coronary thrombosis Cerebral thrombosis Cerebral hemorrhage Hypertension. Gallbladder disease Liver tumors Congenital anomalies There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed Mesenteric thrombosis. Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, usually the most common adverse reaction Vomiting, occurs in approximately 10% or less of patients during the first cycle Other reactions, as a general rule, are seen much less frequently or only occasionally Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding Spotting Change in menstrual flow Dysmenorrhea Amenorrhea during and after treatment Temporary infertility after discontinuance of treatment Edema Chloasma or melasma which may persist Breast changes tenderness, enlargement, and secretion Change in weight (increase or decrease) Change in cervical erosion and cervical secretion Possible diminution in lactation when given immediately postpartum Cholestatic jaundice Migraine Increase in size of uterine leiomyomata. Rash (allergic) Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening) Intolerance to contact lenses The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome. Cataracts Changes in libido Chorea Changes in appetite Cystitis-like syndrome. Headache. Nervousness Dizziness Hirsutism Loss of scalp hair Erythema multiforme. Erythema nodosum. Hemorrhagic eruption Vaginitis Porphyria Impaired renal function Hemolytic uremic syndrome **OVERDOSAGE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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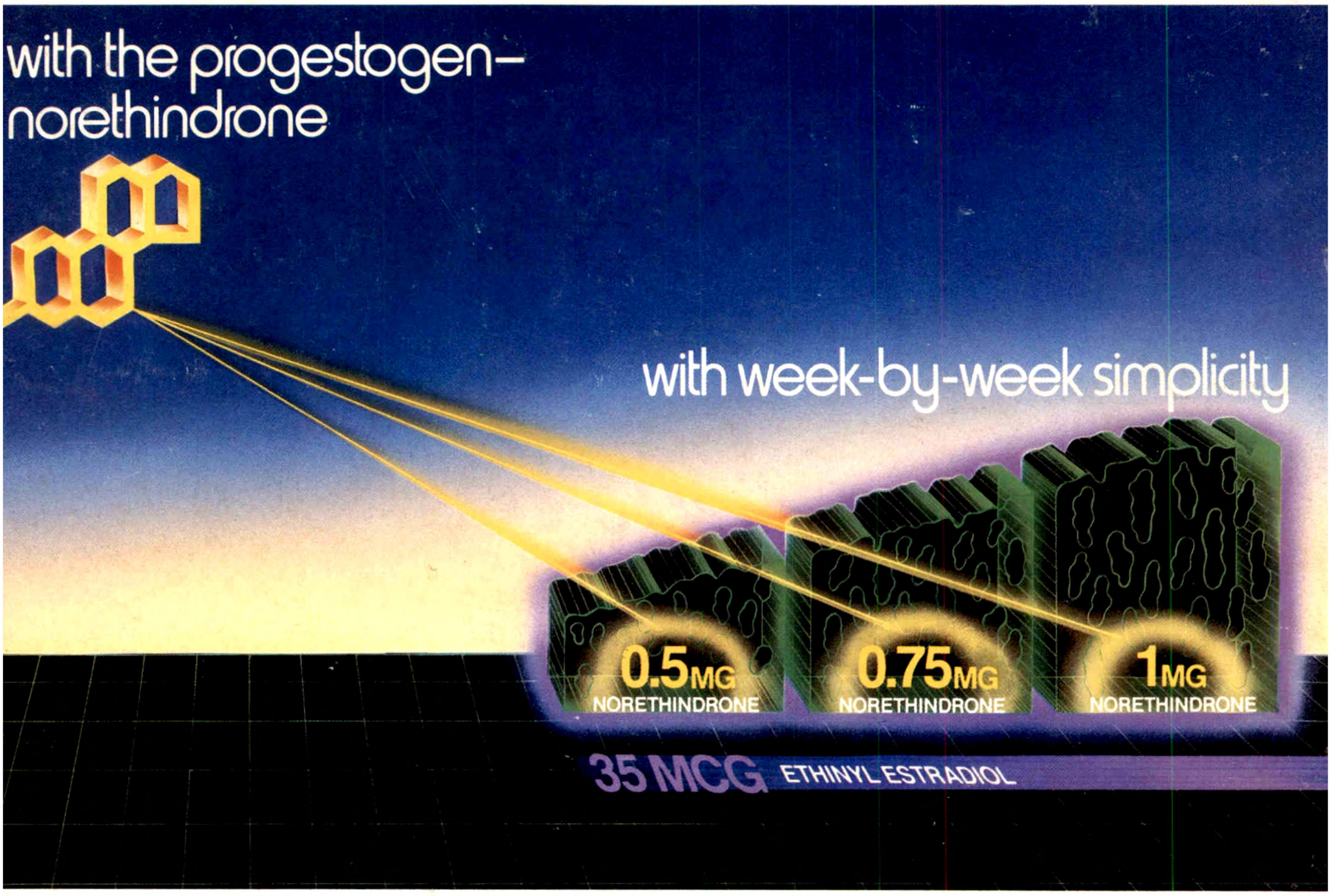

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Indications and Usage: *Treatment*—Serious infections caused by susceptible strains of the designated microorganisms in the following diseases:

LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), other streptococci (excluding enterococci, e.g., *Strep. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Hemophilus influenzae*, and *Bacteroides* species.

GENITOURINARY INFECTIONS. Urinary tract infections caused by *E. coli*, *Klebsiella* species, *Proteus mirabilis*, indole-positive *Proteus* (i.e., *P. morganii*, *P. rettgeri*, and *P. vulgaris*), and *Providencia* species. Uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing).

INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ and *Clostridium* species.

GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by *E. coli*, *N. gonorrhoeae* (penicillinase and non-penicillinase producing), *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and group B streptococci.

SEPTICEMIA caused by *Strep. pneumoniae* (formerly *D. pneumoniae*), *Staph. aureus* (penicillinase and non-penicillinase producing), *E. coli*, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.§

BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to cefoxitin.

Contraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, from mild to life-threatening in severity, has been reported with virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis when diarrhea develops in association with antibiotic use. Broad-spectrum antibiotics alter normal flora of colon and may permit overgrowth of clostridia; a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis. Mild cases may respond to drug discontinuance alone; in more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and use of a drug such as oral vancomycin; isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: Total daily dose should be reduced in patients with reduced urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur from usual doses. Prescribe with caution in patients with a history of gastrointestinal disease, particularly colitis. Prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures. Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Interference with Laboratory Tests—High concentrations (>100 mcg/ml) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. High concentrations may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction and produce false increases of modest degree in levels reported. A false-positive reaction for glucose in urine has been observed with CLINITEST[‖] reagent tablets.

Pregnancy—In women of childbearing potential, weigh anticipated benefit against possible risks.

Nursing Mothers—Cefoxitin is excreted in human milk in low concentrations.

Infants and Children—Safety and efficacy in infants from birth to three months have not yet been established. In children three months and older, higher doses have been associated with increased incidence of eosinophilia and elevated SGOT.

Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reactions*—Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. *Allergic Reactions*—Rash (including exfoliative dermatitis), pruritus, eosinophilia, fever, and other allergic reactions. *Gastrointestinal*—Symptoms of pseudomembranous colitis during or after treatment and, rarely, nausea and vomiting. *Blood*—Transient eosinophilia, leukopenia, neutropenia, hemolytic anemia, and thrombocytopenia; a positive direct Coombs test may develop in some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase. *Renal Function*—Elevations in serum creatinine and/or blood urea nitrogen levels and, rarely, acute renal failure.

Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. The total daily dosage in infants and children should not exceed 12 grams.

How Supplied: Sterile cefoxitin sodium in vials and infusion bottles containing 1 gram or 2 grams cefoxitin equivalent and in 10-gram bulk bottles.

§*B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus*

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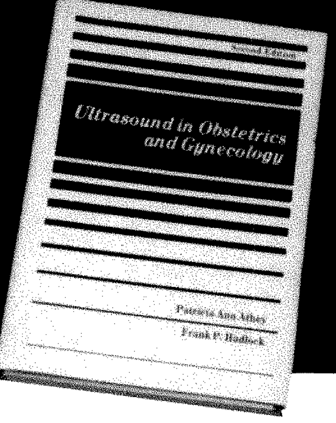

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Contents

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TRANSACTIONS OF THE FIFTY-FIRST ANNUAL MEETING OF THE PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The changing scene 369
Jesse A. Rust, M.D.
San Diego, California

Experience with the pulmonary artery catheter in obstetrics and gynecology 374
Steven L. Clark, M.D., Janet M. Horenstein, M.D., Jeffrey P. Phelan, M.D., Thomas W. Montag, M.D., and Richard H. Paul, M.D.
Los Angeles, California

A return to maternal mortality studies: A necessary effort 379
Leon Parrish Fox, M.D.
San Jose, California

(Contents continued on page 4A)

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Contents continued from page 3A

Lymphatic spread in carcinoma of the vulva 387
David C. Figge, M.D., Hisham K. Tamimi, M.D., and Benjamin E. Greer, M.D.
Seattle, Washington

Sterilization failures and their causes 395
Richard M. Soderstrom, M.D.
Seattle, Washington

Evaluation of the use of continuous lumbar epidural anesthesia for hypertensive pregnant women in labor 404
Thomas R. Moore, M.D., Thomas C. Key, M.D., Laurence S. Reisner, M.D., and Robert Resnik, M.D.
San Diego, California

The significance of meconium in midtrimester genetic amniocentesis 413
Richard Allen, M.D.
Portland, Oregon

Human lymphoblastoid interferon in the treatment of advanced epithelial ovarian malignancies: A Gynecologic Oncology Group study 418
Gazi Abdulhay, M.D., Philip J. DiSaia, M.D., John A. Blessing, Ph.D., and William T. Creasman, M.D.
Portland, Oregon, Irvine, California, Buffalo, New York, and Durham, North Carolina

Twin pregnancy with intrauterine death of one twin 424
John A. Enbom, M.D.
Corvallis, Oregon

Amniotic fluid embolism: An overview and case report 430
Jay I. Mulder, M.D.
Covina, California

Analysis of 2136 genetic amniocenteses: Experience of a single physician 436
Frederick W. Hanson, M.D., Frances R. Tennant, Ph.D., Elinor M. Zorn, M.D., and Steven Samuels, Ph.D.
Davis, California

Abdominal pregnancy: A study of twenty-one consecutive cases 444
Jack G. Hallatt, M.D., and James A. Grove, M.D.
Los Angeles, California

Water-soluble radiocontrast material in the treatment of postoperative ileus 450
Dean T. Watkins, M.D., and Charles L. Robertson, M.D.
Boise, Idaho

Contents

Adnexal torsion 456
Lester T. Hibbard, M.D.
Los Angeles, California

Elevated static pressure and pregnancy well-being 462
R. C. Goodlin, M.D., R. E. Woods, M.D., M. E. McKinney, Ph.D., P. J. Hofschire, M.D., and G. A. Russell-Churchill, R.N.
Omaha, Nebraska

The age extremes for reproduction: Current implications for policy change 467
Ezra C. Davidson, Jr., M.D., and Teiichiro Fukushima, M.D.
Los Angeles, California

Intraperitoneal chemotherapy for advanced ovarian cancer 474
William E. Lucas, M.D., Maurie Markman, M.D., and Stephen B. Howell, M.D.
San Diego, California

The Zavanelli maneuver: A potentially revolutionary method for the resolution of shoulder dystocia 479
Eugene C. Sandberg, M.D.
Stanford, California

Current Development

Neuroendocrinology of opioid peptides and their role in the control of gonadotropin and prolactin secretion 485
S. S. C. Yen, D.Sc., M. E. Quigley, M.D., R. L. Reid, M.D., J. F. Ropert, M.D., and N. S. Cetel, M.D.
La Jolla, California

ITEMS

Items 494

ERRATUM

Correction of article by Cotton et al. 493

Information for authors on pages 11A and 12A

Index to advertisers on page 24A

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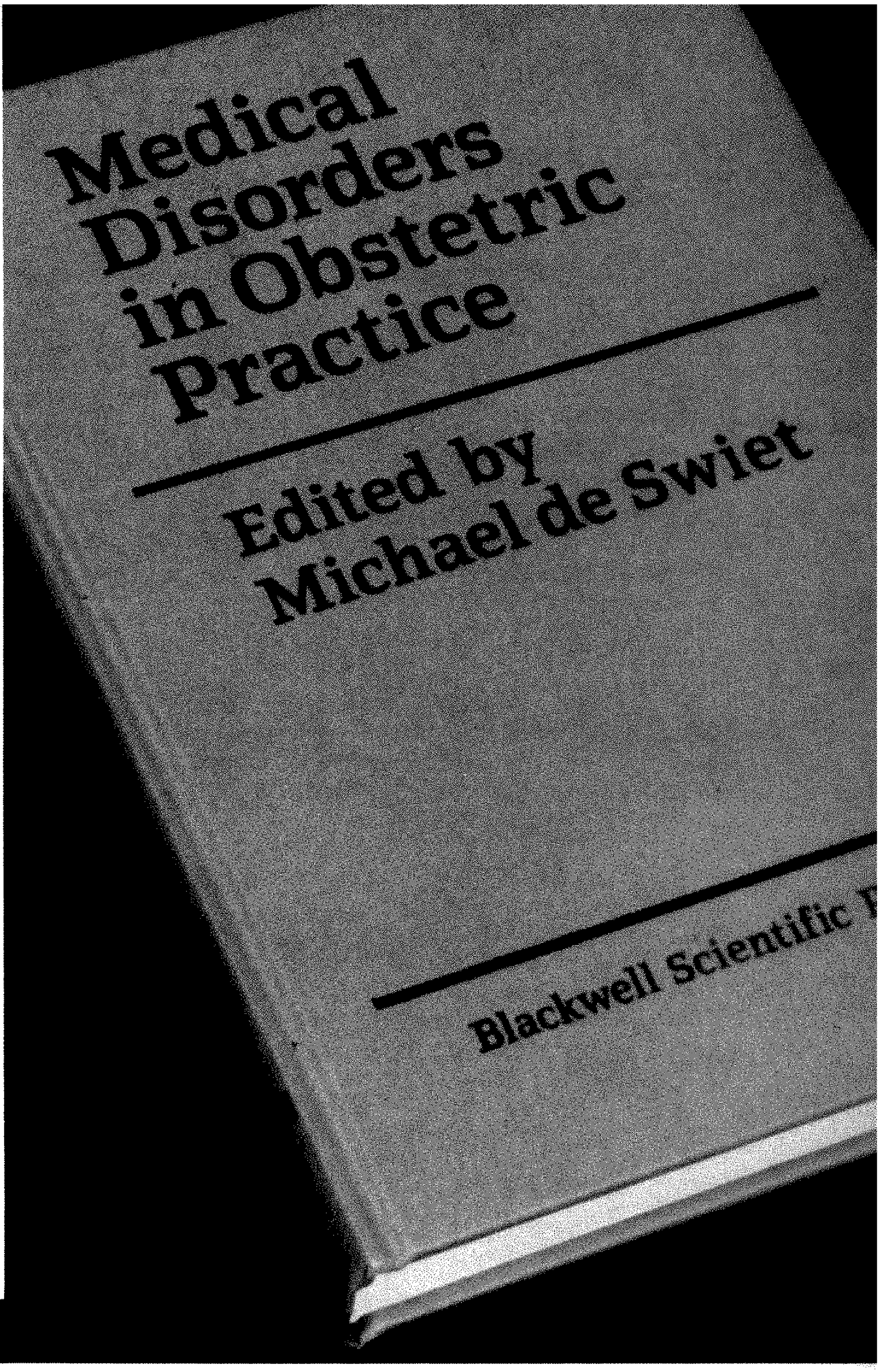
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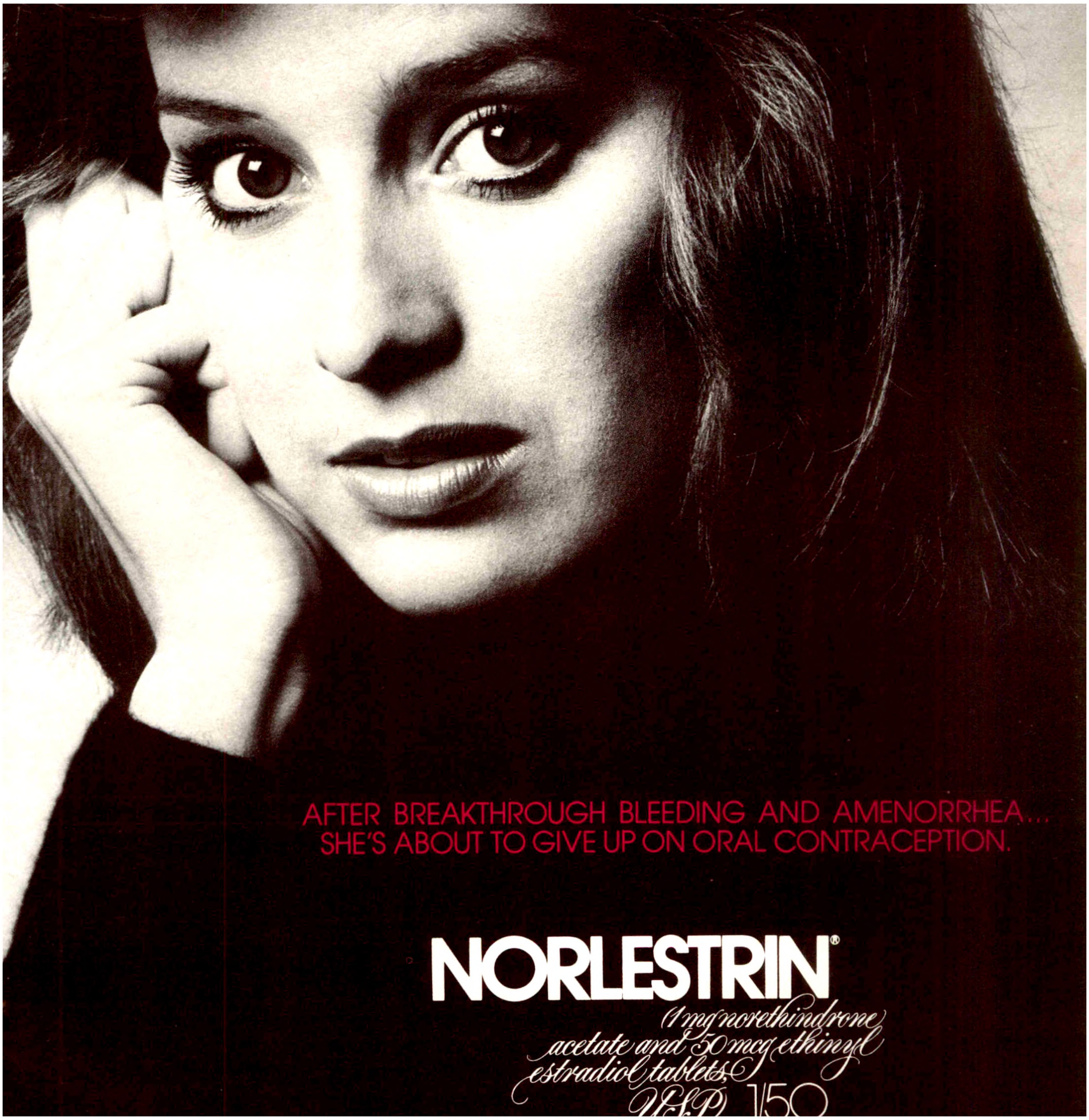
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Brief Summary of Prescribing Information
NORLESTRIN® (norethindrone acetate and ethinyl estradiol tablets, USP)

See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information. A Brief Summary follows.

DESCRIPTION
Norlestrin Products are progestogen-estrogen combinations.

INDICATIONS AND USAGE
Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In clinical trials with Norlestrin 1/50 involving 25.983 therapy cycles, there was a pregnancy rate of 0.05 per 100 woman-years; in clinical trials with Norlestrin 2 5/50 involving 96.388 cycles, there was a pregnancy rate of 0 22 per 100 woman-years.

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance

CONTRAINDICATIONS
1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral vascular or coronary artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (See WARNING No. 5)
8. Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products.

WARNINGS

> **Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.**
>
> The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1 *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombolic stroke was 4 0 to 9.5 times greater

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke The amount of smoking is also an important factor

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction. In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage.

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2 *Ocular Lesions.* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision, onset of proptosis or diplopia; papilledema; or retinal vascular lesions

3. *Carcinoma.* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care

4. *Hepatic Tumors.* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy; Birth Defects in Offspring, and Malignancy in Female Offspring.* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease.* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7 *Carbohydrate and Lipid Metabolic Effects.* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure.* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache.* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives

10. *Bleeding Irregularities.* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy.* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures

12. *Breast-Feeding.* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs

PRECAUTIONS
1 A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.

2 Preexisting uterine leiomyomata may increase in size.

3 Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

4 Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.

5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued

6 Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function

7 Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.

8. Serum folate levels may be depressed.

9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted

10. Certain endocrine and liver function tests and blood components may be affected

(a) Increased sulfobromophthalein retention (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone (d) Decreased pregnanediol excretion (e) Reduced response to metyrapone test.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline and ampicillin

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives thrombophlebitis; pulmonary embolism, coronary thrombosis; cerebral thrombosis; cerebral hemorrhage; hypertension; gallbladder disease; benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed. mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related. nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms; breakthrough bleeding; spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment; temporary infertility after discontinuance of treatment, edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum, cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression, reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted: premenstrual-like syndrome; cataracts; changes in libido; chorea, changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism, loss of scalp hair, erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria

Special Notes on Administration
Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

After several months on treatment, bleeding may be reduced to a point of virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED
Norlestrin 21 1/50 is available in compacts each containing 21 tablets. Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin 21 2 5/50 is available in compacts each containing 21 tablets. Each tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin Fe 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

Norlestrin FE 2.5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets. Each pink tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin 28 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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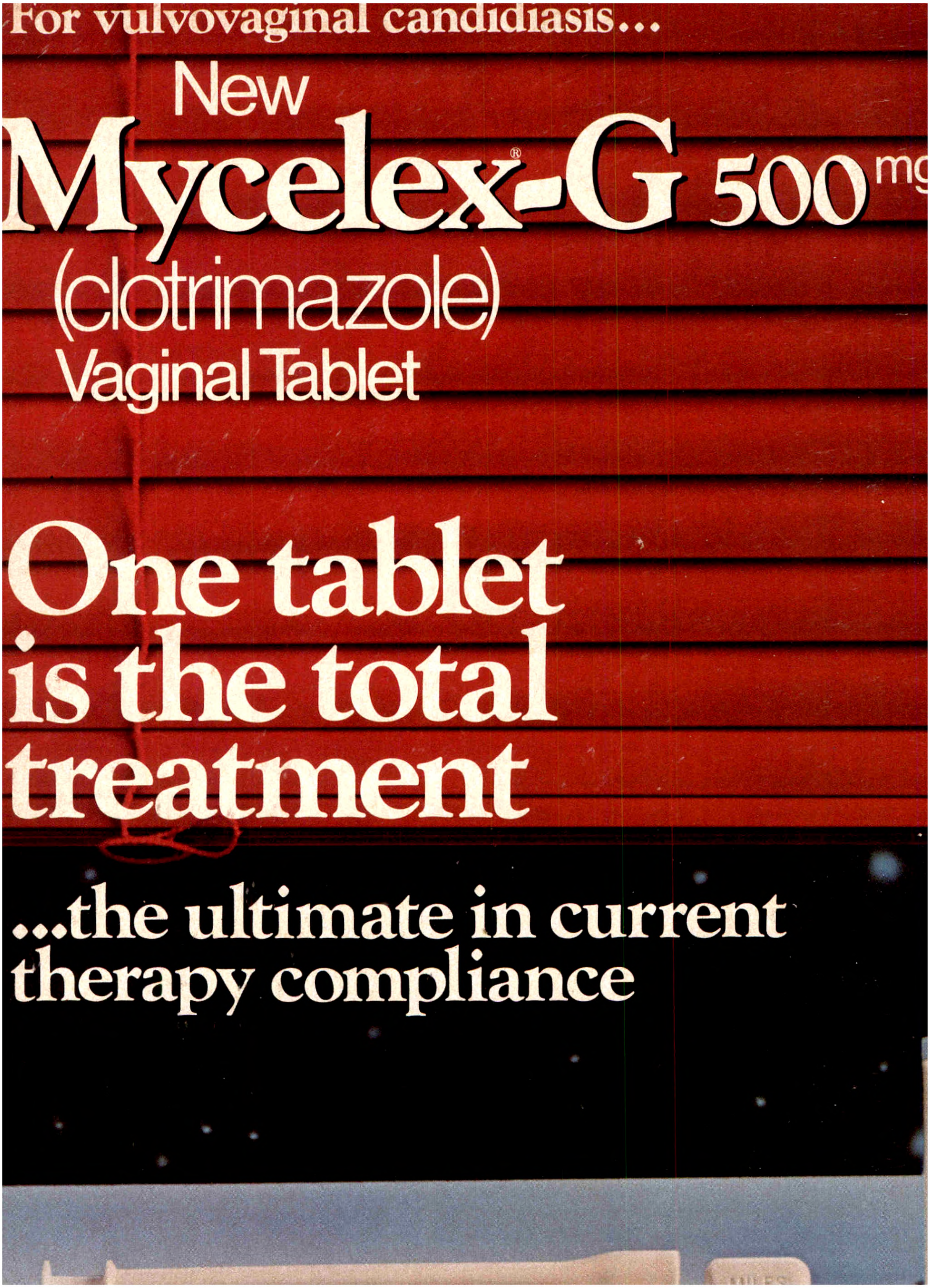

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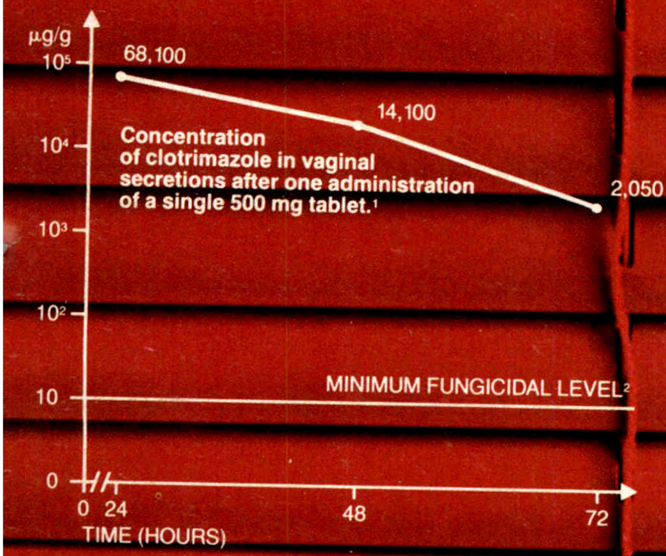

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Repeated high oral doses of clotrimazole in rats and mice ranging from 50 to 120 mg/kg resulted in embryotoxicity (possibly secondary to maternal toxicity), impairment of mating, decreased litter size and number of viable young and decreased pup survival to weaning. However, clotrimazole was not teratogenic in mice, rabbits and rats at oral doses up to 200, 180 and 100 mg/kg, respectively. Oral absorption in the rat amounts to approximately 90% of the administered dose.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly indicated during the first trimester of pregnancy.

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1. Ritter W, Patzschke K, Krause U, et al: Pharmacokinetic fundamentals of vaginal treatment with clotrimazole, *Chemotherapy* 28 (Suppl 1):37, 1982. **2.** Holt RJ, Newman RL: *J Clin Path* 25:1089, 1972. **3.** Mendling W, Plempel M: Vaginal secretion levels after 6 days, 3 days and 1 day of treatment with 100, 200 and 500 mg vaginal tablets of clotrimazole and their therapeutic efficacy. *Chemotherapy* 28 (Suppl 1):43, 1982. **4.** One day treatment of vulvovaginal candidiasis with 500 mg clotrimazole vaginal tablet compared with 3 day regimen of two 100 mg vaginal tablets daily. Summary Report of studies at six centers. Miles Medical Research Report. D82-101, December 23, 1983. **5.** Treatment of vulvovaginal candidiasis with 500 mg clotrimazole vaginal tablet compared with a vehicle tablet. Summary report of multicenter study. Miles Medical Research Report D81-033, December 21, 1983. **6.** Data on file, Medical Department, Miles Pharmaceuticals.

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American Journal of Obstetrics and Gynecology
Founded in 1920
volume 152 number 4 JUNE 15, 1985

TRANSACTIONS OF THE FIFTY-FIRST ANNUAL MEETING OF THE PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The changing scene

Presidential address

Jesse A. Rust, M.D.
San Diego, California

> *The practice of medicine is an art, based on science.*
> *Modern science has made to almost everyone of you the present of a few years.*
> Sir William Osler, *Aphorisms*

Two years after the first annual meeting of this society my first exposure to clinical obstetrics and gynecology occurred. I was a junior medical student at a maternity clinic on the east side of New York City where medical students with little training other than classroom and maniken instruction and a few observed deliveries were sent out to homes as obstetricians. A visiting nurse was there, and a resident was on call for help if needed. Postgraduate experiences included an unusual week spent in Buffalo, New York, with the Potters, father and son, who routinely performed internal podalic version and extraction when the fetal head was well molded and deep in the pelvis, always with the patient under chloroform anesthesia. Postgraduate training and military service were followed by 38 years in private practice in a multispecialty group in San Diego. It seems only reasonable when talking before this prestigious and learned group to recall some personal experiences and to be perhaps somewhat critical of some facets of medicine and of our specialty in particular as I see them today. To go into great depths on any particular subject is not my aim this morning.

As is expected of the president, I have read all the addresses of our past presidents and many of those of other societies and, in addition, have read the history of the first 50 years of this society put together with such dedication by Leon Shulman (with the editorial assistance of Keith Russell). I found all of the addresses to be interesting, especially those in the early years of the organization and those given by people I felt I knew well and respected highly.

Grant Baldwin in 1967 said, "To be president of this society is the greatest honor that will ever come to most of us," with which I agree. And he continued, "but the president is not chosen for his literary ability," with which I also agree, "so why should he be subjected to such a torture as preparing a presidential address?" This I question. Thus 17 years ago he expressed the concern and often the anguish as have six of ten of the immediate past presidents. The year after Charles McLennon in his 1973 address recommended abolishing it, Paul Peterson appointed an ad hoc committee of which all but one, interestingly, were past presidents. The committee unanimously recommended continuation of the address as a "worthy tradition." If I should be on such a committee in the future, I would also vote that way.

As a senior in medical school, I had the enjoyable and rewarding experience of serving as a preceptee

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Presented at the Fifty-first Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Tucson, Arizona, October 21-27, 1984.

Reprint requests: Jesse A. Rust, M.D., 3939 Iowa St., San Diego, CA 92104.

with a Dr. Phelps, an elderly general practitioner in the small city of Vergennes, Vermont. It was the month of March, still winter. I made house calls with him, often in extensive farming regions, and every evening and between house calls we saw patients in his office. One cold but sunny afternoon while driving down a country road plowed for only one-way traffic, we met a team of horses pulling a sleigh loaded with wood. The driver pulled up on the snow bank to let us pass. As we came slowly along side, he recognized his doctor, held his horses, and climbed down. At the end of a brief chat he asked to have his heart checked. A stethoscope was pulled from the little black bag between us, and auscultation was attempted, or rather accomplished, through the sheepskin coat. The patient was informed that his heart sounded the best that it had in a long time. "Thanks a lot, Doc" were his parting words as he climbed back onto his sleigh, obviously very happy. Thus an early exposure to the art of humanistic medicine.

About 1 year after that episode, what I believe to be the most significant milestone to affect the practice of obstetrics and gynecology in my years and perhaps for all times was in the making. It was about 90 years after Oliver Wendell Holmes wrote his monumental paper on "The Contagiousness of Puerperal Fever." I was an intern in a hospital in Poughkeepsie, New York, where there were no residents. Eleanor Roosevelt, wife of the then President Franklin D. Roosevelt, was an occasional visitor to the hospital. On one visit she brought in some sulfanilamide tablets and presented them to the interns. This was before it was available on the market. One of the Roosevelt sons had received it in Boston for a foot infection if I remember correctly. A week or so later, laparotomy on a teenaged girl revealed a general peritonitis from which a pure culture of hemolytic streptococcus was obtained; this was essentially a 100% fatal finding in those days, as were many other infections. With staff approval and nothing to lose, the new medication was administered. Amazingly, she was well in a few days. The introduction of penicillin and other "wonder drugs" was to follow a few years later. It seems reasonable to credit the development of chemotherapy and antibiotic therapy with such benefits in obstetrics as the marked reduction of puerperal sepsis and the safety of today's ±20% cesarean section rate. In gynecology the marked reduction in serious postoperative infections has resulted in total abdominal and vaginal hysterectomies, urinary stress incontinence operations, and other operations being performed, often to improve the quality of life rather than as a last resort for a severe condition. More frequent operations in both obstetrics and gynecology have resulted in improved technical training for so many more obstetric and gynecologic surgeons, which really meant establishing our discipline. I wonder whether vesical/vaginal fistulas would not have been successfully repaired long before Marion Sims' time if infection could have been controlled.

I have mentioned my experiences as a preceptee and as a rotating intern because they were considered by clinical teachers as most significant in the training of a student to practice medicine as a primary care physician. The great majority of obstetricians and gynecologists in private practice are now and probably will always be just that. Today in medical school the student probably has much more patient contact than he did a few years ago. However, I believe the return of some form (and I emphasize, some form) of preceptorship and general rotating internship, not just a surgical rotating internship, would be very beneficial. The internship was often in a different local hospital or even in some other city than that of the medical school. This resulted in a broadening association with doctors from other schools and was a transition period from simply being a student to being accepted as a "real doctor" with more patient contact and a licensed responsibility. It was not infrequently the years in which the career choice was finalized. Preceptorship has always presented the opportunity to learn humanism and the art of medicine from personal experiences with a senior. At one time in history, it was the only form of medical education.

The increasingly limited surgical experience in many of our residency programs is a reason for concern. To return to some type of preceptorship might offer the answer. The alternative would be to increase by double or more the years in residency training if the graduate is to obtain anywhere near the surgical experiences available a few years ago. This is the inevitable result of the cutback in elective surgery, shorter residency hours, vacations, excess number of residents, and the emphasis on science.

In the December, 1982, issue of *Obstetrics and Gynecology* the subject was broadly covered by eight different authors, including a general surgeon and a urologic surgeon. Many different avenues were suggested. An improved modified preceptorship type of training, however, was not considered.

Seriously high complication rates from major gynecologic surgical procedures still exist and should be reduced. However, cesarean section is the safest general abdominal operation performed today. Over a half million hysterectomies are performed each year in our country. These numbers would be much lower if serious complication rates were significantly higher. The potentially serious, minor complications offer much room for improvement. To mention a few, for urinary tract injuries, there are the duration of the operation, infections necessitating extensive use of antibiotics and many laboratory tests, blood loss requiring transfusions that should have been unnecessary, and prolonged hospital stays; also, there are usually avoidable later complications of vaginal prolapse, dyspareunia from a badly scarred vaginal vault or poorly reconstructed vagina, and peritoneal adhesions with later intestinal obstructions and possibly impaired ovarian circulation. All of these and others would be less common with improved techniques.

The early gynecologists were general surgeons with special interest in pelvic surgery. It seems to me, as a result of my World War II experiences, that anyone with technical inclinations can be taught the mechanics of a surgical procedure, but there are many variables in gynecologic surgery that call for technique adaptation. Some people cannot drive a nail straight into a board, yet others are extremely skillful. The former should be recognized in the early years of training and encouraged to extend their abilities in other directions. For surgical quality control in our discipline, the residents showing technical capability should have much more experience in the operating room as the operator as well as the assistant. Possibly on their Board certificates there should be in fine print "Has demonstrated special ability in pelvic surgery." Continuing medical education courses have little to offer in improvement of surgical technique. Whenever possible as a resident and later in practice, one should scrub for one's patient undergoing a pelvic operation by an oncologist, general surgeon, or urologist, none of whom have ever been considered as primary care physicians and who usually will not have to care for the patient after a relatively short period after the operation. In most cases it is not necessary that the gynecologic surgeon be trained or expected to perform all of these operations.

Now that we are considering devoting at least a small part of our programs to what I will call the business of medicine, some remarks on the subject seem to be in order. To do the best for the patient has always been and certainly should continue to be paramount. Will it continue to be? The field of medicine has definitely entered the competitive market place, often influenced and directed by astute business people at both local and national levels. Time was when private practice was the aim of most physicians. Ralph Walker's 1975 presidential address on the requiem of private practice was pessimistic. Today the cost of starting private practice, especially solo, is almost prohibitive for the obstetrician-gynecologist with the totally unreasonable high cost of malpractice insurance and perhaps even more important, the increasingly stiff competition for the patient, especially in a desirable urban community.

The advantages to the patients and the obstetrician and gynecologists of the single specialty groups or multispecialty groups became quite obvious soon after World War II. Both provided more available and expensive equipment, full-time coverage, time for meeting attendance, vacation, and more time with one's family, all of which were increasingly desirable. However, personal responsibility of patient care did not diminish. Very importantly too, group practice facilitated office-performed minor gynecologic surgery. This led to Purvis Martin's organizing of the multispecialty Society for Office-Based Surgery, which has been growing by leaps and bounds since its inception 6 years ago. Now some insurance companies will reimburse the surgeon more for an operation done in his office than in a hospital. However, it is still a problem to get adequate reimbursement for an expensive office surgical suite. How different from the days when, even for a dilatation and curettage, admission to the hospital the day before was required and the patient might stay one or more days afterward. Mention of office surgery brings to mind an amusing incident that occurred at one of the earlier midwinter assemblies in Los Angeles. Soon after a paper from San Diego had been presented on office dilatation and curettages, a group of four or five of us were relaxing late one evening in a booth in the Los Angeles Ambassador Hotel lobby when Ernest Page (our president in 1971) stopped by. With a smile he asked whether the "San Diego Abortionists" were having a meeting. This was long before the 1973 Supreme Court action legalized abortion.

The multispecialty group to which I belong is continuing fee-for-service care but is also successfully bidding on prepaid plans. Incidentally, in the 1950s the first prepaid medical group in San Diego won a law suit to join our county medical society, and soon after two of their very capable obstetrician-gynecologists were admitted to the San Diego Gynecological Society. Human nature being what it is, two levels of care are inevitable; one, necessary, and the other, luxury. Both levels can dispense quality medical care. The only question is the cost and who is paying for it, which makes a big difference. It is the professed aim of the profit-oriented health maintenance organization to cut cost without sacrificing quality. An example that I think worthy of mention is that of a 36-year-old fee-for-service patient who wanted to have a hysterectomy for a number of reasons, all of which were relatively minor but with significant indications for the improvement of quality of her life. She underwent a vaginal hysterectomy after a colposcopic biopsy diagnosis of marked cervical dysplasia bordering on carcinoma in situ. Had this patient been on a prepaid plan, she would have had cryosurgery or conization, and thus possibly hysterectomy would be delayed to a future date when she might be on a different insurance plan or when more serious trouble developed. She had received what I consider to be indicated luxury medical care. Fee-for-service medicine has always existed and still amounts to between 80% to 90% of all medical care. In England it has continued to exist and is increasing under the nationalized health program. It will inevitably remain considerably more expensive. Companies selling fee-for-service insurance with the cooperation of doctors are attempting to meet the competition, not entirely by raising premiums but by reducing costs, especially in hospital care. Business people are possibly less concerned about the quality of care and certainly less concerned about luxury care. They wish to purchase medical care much as they do raw materials. Hence, the bidding goes on.

American medicine is at a crossroad. What has always been care for the sick at all times regardless of the ability to pay is perhaps no longer possible. There is an increasing number of patients in the advanced age group in whom the higher technical advancements have been made for which the cost is astronomic. Who will pay for it? The more affluent will carry fee-for-service insurance, but for the great majority triage will very likely be in order. This has been true in England since the inception of their state medical program. Where will urinary stress incontinence cases, vaginal relaxations, and the troublesome recurrent dysfunctional uterine bleeding in younger patients fit? Gynecologists have been criticized or accused of doing unnecessary surgery, particularly hysterectomies. These critics should hear the sincerely enthusiastic answer of the patient who underwent hysterectomy for dysfunctional uterine bleeding when asked 1 year later if she would like her uterus back or an organ transfer. The response is both entertaining and gratifying.

It seems that in the future there will be an increasing need to utilize patients of the clinical staff particularly in the training of surgery, humanism, and the art of medicine. However, now members of the academic staff rarely serve in a full-time capacity as they become more involved with a personal private practice rather than relying on referred patients. Ivan Langley in his presidential address 2 years ago said that he had written an essay on the "clinical professor." He discarded it for a number of reasons, one of which was the possibility of too many biases. I would like to have read that essay, since I am sure he had an excellent understanding of the changing scenario. The president of Harvard University, Derek Bok, in his very lengthy address on medical education given to the board of overseers in 1982 said, "Teaching hospitals need academic physicians who can attract patients and fill beds, and rapidly growing faculty practice plans offer lots of money to physicians who can do just that." Robert Petersdorf, Dean of the School of Medicine at the University of California at San Diego, discussing medical education along a similar line is quoted as saying, "Medical schools will need two types of faculty. One will practice and the other will do science. Both will teach. They are bound to support one another." This, of course, is a big change from the era when much of the teaching of clinical subjects was done by unsalaried physicians.

The clinical attending teaching staff offers the trainee valuable information on the problems and rewards of patient care outside the institution. The practicing obstetrician-gynecologist is in a position to impart this information to the residents, especially if he has been in practice for more than a few years. The one in practice for a longer period often cares for more than one generation in a family and may follow patients not for 1 year but for many. Also very important, if he is teaching, he is in a position to learn. To teach is admittedly one of the best ways to learn. Certainly all patients should benefit from the continual exposure of the clinician to students, residents, and academic people. For years the clinical staff has served without direct financial rewards, thus keeping the cost of medical education down. Its rewards were real but mostly intangible, such as prestige, personal satisfaction, and an occasional patient referral, often a student's or resident's spouse or relative.

It has been said that progress depends upon changes in the hope that things can always be better. Note our recent questionnaire on the future goals of our society. Certainly no one can belittle the fantastic progress and contributions that have been accomplished in the science of obstetrics and gynecology in the last three or four decades. The value of research in all phases of medicine should not be underestimated or overestimated. From what I have said, I do not mean to indicate in any way a failure to appreciate the great accomplishments. However, to look back and incorporate some of the old with the new could well be to everyone's advantage.

This morning I have had the opportunity to let off a little steam, which Will Rogers is quoted as having said, "only clouds up the windows."

One of my last and most unforgettable house calls was in my second or third year of practice on a mid–Sunday afternoon. The urgent call came through our answering service. A woman was in severe abdominal pain. I must come at once and help her. In those days, there were no emergency services such as those of today. I tried to have someone take her to the hospital, to no avail. After a 5- or 6-mile drive, I found the address in the middle of a Navy housing project. A man standing on the curb urged me to hurry because the woman was in bad shape and suffering terribly. In the bedroom two or three women were standing around a bed on which a young woman was lying with her knees pulled up with a sheet over them. Beneath the sheet a large baby was crying vigorously, the cord still attached to the retained placenta. As I pulled back the sheet, my question was "Why didn't anyone say she was having a baby?" The mother looked up at me and emphatically replied, "That's not my baby. I couldn't have one. My husband's been overseas too long."

I hope and pray that this society will continue to flourish, as it was conceived over half a century ago, as a forum for the distribution of the latest scientific information pertaining to obstetrics and gynecology and for the close personal social relationship of its members.

Experience with the pulmonary artery catheter in obstetrics and gynecology

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Although traditionally the exclusive domain of other medical specialties, pulmonary artery catheterization may be of tremendous benefit to a variety of obstetric and gynecologic patients. Our experience with such invasive hemodynamic monitoring in 72 patients in an obstetrics and gynecology service is presented. In 86% of cases, catheter placement and primary management were carried out by residents in obstetrics and gynecology. Although many of the indications for pulmonary artery catheterization encountered are common to other areas of medicine, certain conditions such as severe preeclampsia or rheumatic heart disease in pregnancy involve pathophysiologic conditions unique to our specialty. On the basis of our experience, recommended indications for pulmonary artery catheterization in obstetric and gynecologic patients are presented. Insertion techniques, complications, and clinical outcome are discussed. (AM J OBSTET GYNECOL 1985;152:374-8.)

Key words: Pulmonary artery catheter, Swan-Ganz catheter, hemodynamics, critical care

Since the introduction of its use in clinical medicine the pulmonary artery catheter has come to play an indispensable role in the management of critically ill patients with cardiovascular compromise.[1,2] Such invasive monitoring procedures have traditionally been the domain of the cardiologist, anesthesiologist, or intensive care specialist. However, our recent experience has suggested that under certain conditions the application of such technique may prove essential in the management of a number of critically ill obstetric and gynecologic patients. Although many of these patients suffer from conditions common to critically ill patients in other specialties, a number of patients will also be encountered with pathophysiologic conditions unique to our specialty. Under such circumstances, optimal patient care is predicated on the obstetrician-gynecologist's understanding of indications for and application of pulmonary artery catheterization.

We present here our experience with the aggressive application of invasive cardiovascular monitoring in an obstetrics and gynecology service.

Material and methods

Women's Hospital is a large county institution with 16,500 deliveries, 5400 admissions to the gynecology (benign) service, and 480 admissions to the gynecologic oncology service annually. In September 1983 a 24-hour critical care service was established under the direction of one of us (S. L. C.) in the department of obstetrics and gynecology. The purpose of this service was to provide consultation including, where indicated, pulmonary artery catheterization for critically ill patients admitted to Women's Hospital. Patients were cared for primarily in the Women's Hospital intensive care unit. However, laboring patients were managed in a special intensive care section of the labor and delivery suite.

Written informed consent was obtained from patients undergoing pulmonary artery catheterization. With use of a strict aseptic technique, a Fr. 8.5 percutaneous introducer sheath (Arrow) was inserted into the internal jugular or subclavian vein by means of the Seldinger technique or into an antecubital vein by means of a venous cutdown. A Fr. 7 Swan-Ganz pulmonary artery catheter was then introduced through the sheath and advanced to wedge position by observing waveform changes. A slow infusion of a dilute heparin solution (CFS Intraflow, Sorenson Research Company) was used to maintain catheter patency. Physiologic monitoring and trace recording were performed with use of a variety of instrumentation (Physiocontrol, Datascope, Hewlett-Packard). Cardiac output determination was by thermodilution by means of a cardiac output computer (American Edwards Laboratories).

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Table I. Indications for pulmonary artery catheterization in obstetric cases

Indication	*No. of patients*	*No. of deaths*
Severe preeclampsia/eclampsia and oliguria or pulmonary edema	13	0
Class III or IV rheumatic/congenital cardiac disease in labor	13	0
Class II or III rheumatic/congenital cardiac disease and severe preeclampsia in labor	3	0
Septic shock	10	2
Adult respiratory distress syndrome	2	0
Amniotic fluid embolism	2	2
Hypovolemic shock unresponsive to fluid replacement	1	0
Other*	3	1
Total	47	6 (13%)

*One case with each of the following indications: pulmonary hypertension and respiratory failure secondary to end-stage tuberculosis, not in labor (died); cesarean section with thyroid storm; congestive heart failure with atrial flutter, not in labor.

Table II. Indications for pulmonary artery catheterization in gynecologic oncology cases

Indication	*No. of patients*	*No. of deaths*
Pulmonary edema of uncertain origin	6	3
Prior to radical surgery with preexisting cardiovascular compromise	6	1
Septic shock	5	1
Shock of unknown etiology	2	0
Total	19	5 (26%)

Table III. Indications for pulmonary artery catheterization in gynecologic (benign) cases

Indication	*No. of patients*	*No. of deaths*
Myocardial infarction	2	0
Septic shock	2	0
Adult respiratory distress syndrome	1	1
Prior to surgery (chronic renal failure and severe hypertension)	1	0
Total	6	1 (17%)

All patients had a chest x-ray examination immediately following catheter insertion.

Most of the procedures were performed by residents of the Department of Obstetrics and Gynecology under the direct supervision of S. L. C.

Indications for pulmonary artery catheterization, techniques, complications, and clinical outcome were examined prospectively.

Results

Over a 1-year period, pulmonary artery catheterization was performed 75 times in 72 patients. This included 47 patients from the obstetrics service (0.3% of admissions), 19 patients from the gynecology/oncology service (4% of admissions), and 6 patients from the gynecology service (0.1% of admissions). Indications for catheter placement in patients from the three services are described in Tables I, II, and III. The mean patient age was 25 years for the obstetric patients, 36 years for the gynecology patients, and 58 years for the gynecologic oncology patients.

The preferred route of insertion (81%) was the right internal jugular vein (Table IV). This procedure was performed by residents in obstetrics and gynecology under direct supervision of S. L. C. in 65 cases (86%). In 10 cases (14%) such supervision was not available, and catheterization was performed by the departments of internal medicine or anesthesiology. Of 75 procedures, 71 (95%) were performed in an intensive care unit setting whereas 4 (5%) were performed in the operating room.

Complications of introducer and/or catheter insertion are listed in Table V. One or more premature ventricular contractions were encountered in 20 patients (27%) during passage of the catheter through the right ventricle. Prophylactic lidocaine was not routinely employed. However, two patients received such therapy (1 mg/kg intravenously) because of preexisting ectopy and two prior to repassage following catheter withdrawal for coupled premature ventricular contractions. In no case was inadvertent arterial puncture associated with significant bleeding or subsequent morbidity. One pneumothorax resulted from subclavian catheter placement. This was small and clinically insignificant and was detected only on routine chest x-ray examination following placement. We observed no pulmonary infarction, life-threatening arrythmias, venous thrombosis, or catheter-related sepsis.

In the obstetric patients catheters remained in place for a mean of 2 days (range, 1 to 12) compared to a mean of 4 days (range, 1 to 16) for the patients from the two other services. A single catheter-introducer was left in place for a maximum of 8 days. Catheter malfunction occurred in three cases (5%) (two balloon-related malfunctions and one Thermistor-related one).

Twelve patients (17%) undergoing pulmonary artery catheterization died of their underlying disease processes prior to discharge from the intensive care unit (Tables I to III). In no case was the catheter implicated in either death or long-term morbidity.

In 27 patients (38%) central venous pressure and

Table IV. Route of venous insertion in pulmonary artery catheterization

Route	*No. of insertions*	%
Right internal jugular	61	81
Right subclavian	9	12
Left internal jugular	2	3
Left subclavian	2	3
Right antecubital	1	1
Total	75	100

pulmonary capillary wedge pressure differed by ≥10 mm Hg, either initially or during the course of therapy. This included 14 of 15 pregnant patients with cardiac disease (93%), 4 of 16 patients with septic shock (25%), and 2 of 17 patients with severe preeclampsia (12%).

Comment

First introduced by Swan and Ganz in the early 1970's,[1] the flow-directed pulmonary artery catheter has found widespread utility in many areas of medical and surgical critical care. Techniques of line placement, associated waveform changes, and applicable hemodynamic theory have been described elsewhere.[3]

Many indications for pulmonary artery catheterization encountered in obstetric and gynecologic cases are common to other areas of medicine. These include some subsets of acute myocardial infarction,[1] pulmonary edema of unknown etiology, adult respiratory distress syndrome in certain patients,[5] septic shock, or radical surgical procedures.[6] In addition, two major groups of patients were encountered whose pathophysiology is unique to the field of obstetrics. These conditions warrant further comment.

Severe preeclampsia is a condition characterized by intense peripheral vasospasm and intravascular volume depletion. In such patients oliguria is not an uncommon clinical finding. In our experience such oliguria is usually on the basis of simple hypovolemia (low pulmonary capillary wedge pressure, moderately increased systemic vascular resistance, and hyperdynamic left ventricular function) and will respond to fluid therapy alone. Less often, oliguria is secondary to intense peripheral vasospasm with impending left ventricular failure (high pulmonary capillary wedge pressure, markedly elevated systemic vascular resistance, and depressed left ventricular function) and is treated by fluid restriction and afterload reduction with vasodilators. These two conditions may be clinically indistinguishable. The central venous pressure may also be low in either case; central venous pressure has been shown to be a poor indicator of left ventricular preload as assessed by pulmonary capillary wedge pressure in a significant number of preeclamptic patients.[7,8] Thus while invasive hemodynamic monitoring is not indicated in the majority of patients with severe preeclampsia, we feel pulmonary artery catheterization is essential in the patient with persistent oliguria if proper therapy is to be instituted and fluid overload, with pulmonary or cerebral edema, avoided. Benedetti has shown that alterations in hydrostatic pressure, plasma colloid osmotic pressure, and pulmonary capillary permeability all may be implicated in the genesis of pulmonary edema in patients with severe preeclampsia.[9] We have found hemodynamic assessment by means of the pulmonary artery catheter to be invaluable in differentiating the mechanism of pulmonary edema in such patients and in guiding subsequent therapy.

Table V. Complications in pulmonary artery catheterization in obstetrics and gynecology

Complication	*No. placed by obstetric and gynecologic service (n = 65)*	*No. placed by other services (n = 10)*	*Total (%)*
Premature ventricular contractions	17	3	27
Arterial puncture	5	1	8
Superficial cellulitis	2	0	3
Pneumothorax	0	1	1

Significant hemodynamic changes accompany normal pregnancy and the peripartum period. These have been discussed in detail elsewhere.[10, 11] Of particular concern are the marked fluctuations in hemodynamics which occur during normal labor and delivery, including a postpartum "auto-transfusion" phenomenon in which cardiac output increases up to 65%. Patients with structural cardiac defects may be unable to increase their cardiac output to this degree, resulting in pulmonary edema during the immediate postpartum period. Patients with a significant degree of pulmonary hypertension are additionally vulnerable to decreases in venous return and right ventricular preload, which may result in decreased perfusion of the pulmonary vascular bed. Pulmonary artery catheterization during labor and delivery allows the clinician to optimize ventricular preload and cardiac output in order to avoid pulmonary edema or hypotension during the intrapartum period as well as to prevent postpartum pulmonary edema. It must be emphasized that assessment of central venous pressure alone is a poor indicator of true left ventricular end-diastolic pressures in the majority of pregnant patients with cardiac disease.

Eighty-one percent of patients underwent catheterization via the right internal jugular vein. We prefer this route over subclavian vein puncture for two reasons. First, pneumothorax may be less likely to occur.

Second, should inadvertent arterial puncture occur, the carotid artery is more amenable to hemostatis via direct pressure than is the retroclavicular subclavian artery. The subclavian route is, however, a useful alternative. The single brachial cutdown was performed for pulmonary artery catheterization in a patient with a platelet count of 8000/ml. Although it is more difficult and time consuming, such an approach is mandatory in a patient in whom laceration of a major vein or inadvertent arterial puncture could be life-threatening.

The rate of complications encountered during catheter placement by the obstetrics and gynecology service is comparable to that experienced in other critical care settings. Ventricular ectopy during passage of the catheter tip through the right ventricle is a common, and generally benign, occurrence. Our incidence of premature ventricular contractions (27%) compares with 15% to 78% in other series.[12, 13] Our 3% incidence of superficial cellulitis compares with 16% in another large series.[12] This difference may be attributed to the relatively short duration of catheterization required in the present series; Sise et al.[12] showed that, with a duration of catheterization of <72 hours, such site complications were almost nonexistent. The rate of inadvertent arterial puncture of 8% is somewhat higher than the 3% to 5% usually reported.[12] The fact that most of the procedures were performed by residents in training may account for this difference. Pneumothorax is reported in from 0% to 6% of central venous catheterizations.[12, 14] Our single subclinical pneumothorax falls well within this range. The absence of major complications in this series attests to the relative safety of this procedure in experienced hands.

Potential complications of pulmonary artery catheterization per se include pulmonary artery rupture, pulmonary infarction, papillary muscle damage, and lethal arrythmias. On the other hand, pneumothorax, arterial puncture, and superficial cellulitis are complications of obtaining central venous access. Our data would suggest that in practice the principle morbidity associated with pulmonary artery catheterization is primarily that of obtaining central venous access and would be similar whether simple monitoring of central venous pressure or pulmonary artery catheterization were used. Thus when central hemodynamic monitoring is indicated and the trained personnel and equipment required for pulmonary artery catheterization are available, the additional information obtained by advancing a catheter to the pulmonary artery would in most cases outweigh the small additional risk of this procedure. Under such circumstances there would appear to be very few indications for central venous pressure monitoring alone.

The establishment of an independent capability for such invasive hemodynamic monitoring within an obstetric and gynecologic service has several unique advantages. Consolidation of care will primarily benefit the seriously ill patient with an underlying condition whose pathophysiology is unique to pregnancy. If such a patient requires invasive hemodynamic monitoring, she may be best served if her physicians both thoroughly understand the underlying condition and are skilled with the application of such monitoring techniques. In addition, monitoring of fetal well-being in the critically ill mother is seldom optimal in a medical or surgical intensive care unit. Finally, critically ill obstetric and gynecologic patients may require both medical and surgical intervention. We recently managed a patient who presented to the hospital in severe septic shock secondary to a pelvic abscess. This patient was admitted to the obstetrics and gynecology intensive care unit where hemodynamic management was guided by a pulmonary artery catheter. After the patient's blood pressure had been stabilized on high-dose dopamine, we were able to take her immediately to the operating room for colpotomy drainage. The patient subsequently recovered fully. In such a case, delay or inefficiency in instituting either medical or surgical therapy might have been fatal. Such delay would have been more likely had transfers and consultation between several services and wards been necessary. The establishment of such a service requires an intensive care unit with properly trained nurses, appropriate equipment, and physicians with the necessary clinical skill to place and troubleshoot central lines. In addition, a patient population sufficient to require the placement of at least 2 to 3 pulmonary artery catheters a month, either clinically or under a research protocol, would seem necessary for the involved physicians to maintain sufficient clinical skills to place and manage these lines safely and correctly. When these conditions cannot be met, placement and primary management of pulmonary artery catheter by the obstetrician-gynecologist is probably not a realistic goal. In such situations, the obstetrician-gynecologist who is familiar with indications for pulmonary artery catheterization and who can combine a knowledge of obstetrics and gynecology with a basic understanding of the central hemodynamic disturbances he is likely to encounter will provide optimal care for his patients in consultation with the anesthesiologist or internist. In experienced hands, pulmonary artery catheterization is safe and, when indicated, may be of significant benefit to a variety of obstetric and gynecologic patients.

Addendum

In the 6 months since the initial compilation of our experience, an additional 18 patients have undergone pulmonary artery catheterization to assist in clinical management. Indications in nine obstetric patients were: severe preeclampsia associated with persistent oliguria or pulmonary edema, four; New York Heart Association Class III or IV cardiac disease during delivery, three; and septic shock, two. Indications in four patients from the gynecology service (benign conditions) were: preoperative evaluation in patients with preexisting cardiac disease, two; septic shock, one; and congestive heart failure, one. Five patients from the gynecologic oncology service underwent catheterization for septic shock (two) and pulmonary edema of uncertain origin (three). Complications encountered during these additional procedures were arterial puncture in one patient, premature ventricular contractions in five patients, and superficial cellulitis in one patient. Clinically significant morbidity associated with this procedure remained nil. The addition of this experience to include 90 patients during an 18-month period did not significantly alter the complication rates reported in the original manuscript.

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A return to maternal mortality studies: A necessary effort

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This report reviews the experience of the Santa Clara County Maternal Mortality Study Committee, which continued its local activity after the termination of California state-supported study groups in 1970. A study of 36 maternal deaths among approximately 262,000 live births was compiled over a 13-year period, between 1971 and 1983, in a population group representative of much of California. Although based on a small population sample, the results indicate an imperative need for such reviews to improve the quality of clinical care and to develop significant statistical information on the incidence and causes of maternal mortality. The historical development of study committees throughout the United States illustrates the necessity of standardized definitions and uniform methodology among study groups in all states and territories. A nationwide study is proposed to obtain a broad-based, cumulative maternal mortality series, directed toward the eventual elimination of preventable maternal deaths. The current effort by a special interest group in the American College of Obstetricians and Gynecologists is commended for beginning this task. (AM J OBSTET GYNECOL 1985;152:379-86.)

Key words: Maternal mortality, committee studies

Peer review has become a generally accepted method for preserving disciplinary standards of medical practice in the United States. Maternal mortality study committees, a pioneer concept in this tradition, exemplify the effectiveness and values of the peer review system. Historically the development of maternal mortality study groups in the United States was the result of almost 15 years of discussion and planning by leaders such as P. F. Williams and G. W. Kosmak, who enlisted the aid of national, state, and county organizations in encouraging an analysis of all maternal deaths nationwide. The publication of early studies from New York (1933), Philadelphia (1934), and the Pacific Coast region (1935) stimulated much interest in this effort, and in 1948 the American Medical Association established a Committee on Maternal and Child Care. The *Guide for Maternal Death Studies* published by this committee provided basic guidelines for the various state and regional study committees that were instituted subsequently.[1]

In California the clinical benefit and educational potential of maternal mortality studies were recognized early in their development. With the impetus provided by Bell's pivotal studies of seven cities of the Pacific Coast in 1933 to 1934, a long-standing commitment to such studies was established in the state. Instigated by Bell, Thompson, Russell, Overstreet, and other prominent practitioners throughout California, a statewide evaluation of all pregnancy-related deaths was initiated in 1957 by the California Medical Association and the California State Department of Health. The California Medical Association Committee on Maternal and Child Health organized six district committees who performed independent, intensive studies to obtain, review, and evaluate case findings according to the definitions, terminology, and procedural methodology outlined in the American Medical Association Guide. These groups then held discussions to identify the immediate and primary cause(s) of death in these cases, differentiating deaths that could be attributed directly or indirectly to obstetric causes from those attributable to nonobstetric causes. Preventable or avoidable factors were assigned in categories related to the patient's personal responsibility, to care by professional attendants, and/or to the facility providing care.[2] During the following 13 years 1582 records were reviewed, computerized, and used for educational purposes; the results are published elsewhere.[3,4]

By 1968, 44 states and the District of Columbia had ongoing maternal mortality committees, some of which had become concentrated in selected metropolitan regions.[1] Since that time, however, participation in such study committees gradually has decreased—in California as well as elsewhere in the United States. A survey by our group indicated that in 1983 there were active committees in 33 states and the District of Columbia (unpublished data). Most of the more recent maternal mortality studies have been conducted under the aegis

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From the Santa Clara County Maternal Mortality Study Committee.
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of individual state committees on maternal and child health.

The causes for this apparent decline in interest in maternal mortality study committees in California no doubt reflect factors that can be extrapolated to the country in general. When the California Medical Association–sponsored committees on maternal and child health began their evaluations in 1957, the number of live births in California was 336,584 in a state population of 12,500,000, and the maternal mortality rate was 35.9 per 100,000 live births. By 1970 the state population had increased to 20,825,000 with 362,652 live births, and the statewide maternal mortality rate had decreased to 21.2 per 100,00. In view of this lower mortality and with cost-effectiveness as a primary consideration, the California State Department of Health discontinued the $60,000 budget item slated for the committees. Because the California Medical Association was unable to underwrite the amount required to finance the entire project, the decision resulted in termination of the statewide committees. Although county or regional studies were encouraged and the possibility of developing other projects for the committees was discussed, effective sponsorship ceased—with little concern regarding obstetric need for the studies or the educational value they afforded.[4]

Certainly, maternal mortality rates in this country have declined progressively during the past half-century, coincident with a surge in general medical knowledge and the significant advances in medical care represented by developments in blood transfusion, antibiotics, anesthesia, and technological instrumentation (increased hospital deliveries and legalized abortions also having a due share of credit).[5] Although these rates have fluctuated since 1970, there is little doubt about their tendency downward: in 1982 the maternal mortality rate was 11.0 per 100,000 live births. Although this trend provides a fiscally rational basis for the reduction in state and organizational support of maternal mortality study committees, two qualifying points bear consideration. There remains an unequivocal need to review and foster improvement in patient care, objectives that are basic to the purpose of such study committees. Equally important is the fact that there are many areas in which answers to puzzling obstetric problems may be revealed by widespread maternal mortality studies. To cite only one example, it is now evident that some pregnant women have a lowered resistance to the leading causes of maternal deaths: hemorrhage, infection, and toxemia. These conditions historically have been the dominant direct cause of death in such patients; frequently one or more of the triad joins the primary condition to overwhelm the victim's immunologic defenses. Through the dramatic developments in our field we have been able to improve these patients' resistance, but we have not defined the mechanism of this immunologic dysfunction that may accompany pregnancy.

In view of the potential contributions to patient care and obstetric medicine that maternal mortality reviews represented, several counties in California attempted to continue local studies after the statewide maternal mortality committees were disbanded in 1970. Although these efforts were largely unsuccessful, the study committee developed in Santa Clara County has documented a 13-year review of maternal mortality cases. The results of this series are presented here as initial data to be augmented by frequent publications of data gathered from similar groups and with the ultimate goal of encouraging nationwide studies in which obstetric deaths are evaluated substantively and in a uniform manner.[3-7]

Background and organization of the study group

The Santa Clara County Maternal Mortality Study Committee, modeled after the divisional committees of the California state network that was abolished in 1970, was formed to continue evaluations of comparable quality on a county-wide basis. Developed under the joint sponsorship of the Shufelt Gynecologic Society of Santa Clara Valley and the Santa Clara County Medical Society, the committee adopted the procedures followed by the earlier state committees and is assured the same legislative immunity granted to those committees.

The study committee consists of nine general obstetricians (including the chairman), two obstetrician-perinatologists, a generalist, an anesthesiologist, an internist-pathologist, a pathologist, and a public health physician. An adjunctive panel of consultants includes one public health physician and five additional obstetricians. The committee meets whenever two or more cases have accumulated for review; meetings are held on Saturday mornings and last about 2 hours. Attendance is excellent.

The committee's sponsors are instrumental in its activities. The personnel and management aid for its studies are provided by the Shufelt Society. The Santa Clara County Medical Society underwrites the paperwork, mailing costs, meeting facilities, and the storage of completed records. The members of the study committee are appointed by the committee chairman with the approval of the president of the Santa Clara County Medical Society; the president recognizes the committee in his roster, and reports of the study committee are submitted to the president on a regular basis. In addition to the enthusiastic support of its sponsors, the study committee has broad-based support in the general medical community and particularly among obste-

Table I. Total number of live births and obstetric deaths during years of study

Year	No. of births registered	Live births		Obstetric deaths
		Resident*	Nonresident	
1971	18,385	17,596	789	1
1972	17,253	16,598	655	1
1973	16,912	16,161	751	3
1974	17,587	16,800	787	3
1975	17,649	16,647	1,002	3
1976	18,380	17,371	1,009	1
1977	19,361	18,140	1,221	2
1978	19,847	18,488	1,359	1
1979	21,169	19,721	1,448	2
1980	22,795	21,245	1,550	0
1981	23,603	21,862	1,741	5
1982	24,336	22,518	1,818	7
1983	24,691	22,633	1,958	2
Total	261,968	245,780	16,088	31

*Patient residence in Santa Clara County.

tricians, teaching faculties, house officers, and students in the county. The active participation and cooperation of this community affords simplicity in organizing and maintaining uninterrupted the data collection and functions of the study group.

Material and methods

The population of Santa Clara County, an industrialized and agricultural community of approximately 1.4 million people, is representative of that in much of California. Over the 13-year period of this study, between 1971 and 1983, the percentage of this population in the Caucasian and Hispanic groups has remained stable at approximately 78% and 17.5%, respectively, while the percentages representing Asian, black, and other ethnic/racial groups have increased.

During the early years of the study, routine case finding was considered less than optimal, and the committee sought more rigorous methods of data collection. With the aid of the local health department and its alert personnel, all death records of women in the childbearing age were then reviewed, with significantly improved results.

The format, forms, and procedures used by the earlier state committees provide the basis for the committee's review process. All records of a maternal death occurring within 90 days of birth or termination of pregnancy for other causes, or of death suggesting a relationship with pregnancy, are reviewed and evaluated by the committee according to the following schema: Each case is investigated by a certified obstetric consultant who has authorized access to the hospital, pathology reports, and physician's records and who is authorized to interview responsible personnel as indicated. All data are submitted to the chairman of the committee, who assigns a case number that is used exclusively for case identification thereafter. The patients' anonymity is protected scrupulously. The material is presented to the study committee by the investigating consultant and the pathologist who has reviewed the autopsy reports and slides. The sequence of the primary and immediate cause(s) of death is established through the committee members' discussion and evaluation of the case. The committee then classifies the death according to whether the cause was obstetric or nonobstetric and, if the cause was obstetric, whether directly or indirectly related to pregnancy. Finally, preventability factors are evaluated as related (1) to the patient's responsibility, (2) to technical and/or judgmental factors, (3) to the care or responsibility of professional attendants, and/or (4) to essential provisions by the facility. Preventability factors are measured against the ideal standards. After the study is concluded and the decisions recorded, a summary is sent confidentially to the physician and/or facility responsible for the patient's care.

Results

The number of live births in our countywide population area during the period of this study ranged from 18,385 in 1971 to 24,691 in 1983, with a total of 261,968 live births. During this 13-year period 36 deaths were judged to be associated with pregnancy among the total number of live births; the group included 31 patients judged to have died from obstetric causes and five patients whose death was determined to be nonobstetric (Table I). The number of cases recorded each year was erratic and therefore statistically nonindicative. It is fortunate that the cases of pregnancy-associated deaths are few; because of the small

Table II. Analysis of deaths studied

Direct cause	*No. of patients*	*Indirect cause*	*No. of patients*	*Total*
Obstetric (n = 31)				
Hemorrhage				9
Abortion	1	Ruptured aortic aneurysm	1	
Uterine, postpartum	1	Ruptured right ovarian vein	1	
Ectopic	5			
Subtotal	7		2	
Toxemia	8			8
Sepsis				5
Abortion	1	Vascular necrosis, perforated colon	1	
Toxemia: cesarean section	1		1	
Choriocarcinoma, hysterectomy	1			
Ruptured liver, toxemia: surgery	1			
Subtotal	4		1	
Pulmonary embolism				4
Amniotic fluid	2			
Fibrin thrombi	1			
Phlebothrombi, postpartum	1			
Subtotal	4			
Cardiovascular				4
Cardiomyopathy, postpartum	1	Abortion, myocarditis, disseminated intravascular coagulation	1	
		Eisenmenger's syndrome	1	
		Ruptured cerebral aneurysm	1	
Subtotal	1		3	
Anesthesia		Epidural bupivacaine	1	1
Total	24		7	
Nonobstetric (n = 5)				
Bronchopneumonia, dementia	1			
Exsanguination, disruption dialysis shunt	1			
Pulmonary embolism phlebitis at 6 weeks	1			
Homicide	2			
Total	5			

study population, however, we cannot discuss the resultant data in terms of statistical significance and must restrict our conclusions only to trends.

The maternal mortality rate for the 13-year period of study was 11.8 per 100,000 live births. An analysis of the 36 deaths is presented in Table II: 24 deaths were attributed directly to obstetric causes, seven were indirectly due to obstetric causes, and five were due to nonobstetric causes. Hemorrhage (seven cases), toxemia (eight cases), and sepsis (four cases) were the major causes of pregnancy deaths, together with death from embolism (four cases). These trends are in agreement with those represented in the most recently published vital statistics report for 1981.[8]

Elements suggesting that death may have been preventable were considered of significant importance in the cases of 28 patients: in 22 of these cases, death was attributed to the likely culpability of professional attendants, four deaths were due to inadequacy of the facility, and 14 were attributed as the patient's responsibility.

The demographic factors related to the obstetric patients studied are shown in Table III. The largest number of deaths in this group were in the Caucasian (15 patients) and Hispanic (10 patients) population groups. Most deaths occurred among women of age 26 to 35 years. Patients with low parity (0 to 1) were predominant, as were married patients. Only five patients died at home, all of catastrophic intra-abdominal hemorrhage. Of the 26 women who died in hospital facilities, 10 were in Level I institutions and 10 others were in Level III institutions affording high-risk facilities; 10 of these women were delivered by cesarean section, three had abortions, seven had ectopic pregnancies, and the other six women had vaginal deliveries in hospitals. There were no home births in the series. The youngest patient, a 16-year-old girl who died of sepsis 133 days post partum after undergoing hysterectomy for advanced choriocarcinoma, is included in the study even though her death exceeded the 90-day limit set for our evaluations. The oldest patient in the study, who was 40 years old, died of toxemia.

The data indicate that the patients at highest risk were Caucasian, nulliparous, married women between 26 to 35 years of age, who were in the last trimester of pregnancy and in the puerperium and were being treated in a hospital facility. In a larger experience this impression may be different.

Comment

The efficacy of maternal mortality committees in reducing maternal mortality has been controversial.[5] Nonetheless, there is reason to suspect that the effectiveness of such committees would become evident if a great majority of maternal deaths were subjected to detailed study. Small sample studies such as ours confirm that preventable maternal deaths still occur in hospitals throughout the United States. Moreover, our results indicate that—despite advances in medical treatment—hemorrhage, infection, and toxemia are still responsible for a major proportion of deaths during pregnancy. These findings reflect a need to resume systematic analyses of the incidence and causes of obstetric mortality. Maternal mortality study committees are a uniquely suitable vehicle for such an effort.

Our experience indicates that peer review is a desirable and effective method by which to maintain standards of obstetric care and that maternal mortality study groups provide a means to alert those who may be unaware of less-than-optimal standards in their facility. Practitioners who participated in the earlier maternal mortality studies recognized the educational value of these retrospective investigations in improving their personal methodology for clinical management and were gratified by their experience.[1] Similarly, our committee's observations have been shared with hospital medical staff, faculty, house officers, medical students, and nursing personnel. The insight and knowledge gained have been rewarding to all concerned—a result for which we are grateful. We have found unequivocally that peer review of this nature not only is instructive but also can instigate constructive corrective action and ultimately result in fewer instances of maternal mortality.

Continual and progressive improvement in case-finding, methods of activity, and effectiveness is needed to attain the objectives of obstetric mortality studies. Two particular problems confront efforts to obtain a true picture of the status and causes of maternal mortality in the United States:

1. Death certificates are used by state departments of health and the National Center for Health Statistics to determine maternal mortality data. Contributing to the inaccuracy of these data is the fact that across the country these documents frequently do not include information showing whether or not a death was related to pregnancy. In our study we found 10% of death certificates in error on this issue, and pertinent information was omitted in 13 of the 36 records reviewed. Rochat[9] has discussed inadequacies inherent to the current reporting of maternal deaths and has suggested corrective methods. Zemach[10] has updated the efforts of the National Center for Health Statistics and state health agencies to improve the vital records system.

Table III. Demographic factors relating to obstetric deaths

Factor	No. of patients
Age (yr)	
15-20	6
21-25	3
26-30	10
31-35	9
36-40	3
Parity	
0	11
1	9
2	4
4	2
5	1
?	4
Trimester	
First	8
Second	1
Third	22
Puerperal	19
Race	
Caucasian	15
Black	3
Hispanic	10
Filipino	2
Japanese	1
Marital status	
Married	22
Single	9
Site of death	
Hospital	
Level I	10
Level II	6
Level III	10
Total	26
Home (ruptured ectopic)	4
Home (ruptured aortic aneurysm)	1
Total	5

2. In major medical centers that have sophisticated intensive care units, occurrence of a rapid turnover of referrals and information regarding obstetric patients in superspecialized divisions, often can become lost in the referral process; for example, extremely ill cardiovascular patients are taken to the cardiac service, renal victims to the nephrology area, and sepsis cases to the infectious disease sector. When such patients die, physicians certifying death may well omit mention of pregnancy status; this is frequently the case when a patient has been maintained on a life-sustaining system for a period of weeks.

Many states and regions have recognized the value of compiling maternal mortality data and the problems involved in obtaining accurate information—and therefore are engaged in improving their recording methods, documentation procedures, and demographic considerations in a standard and uniform manner. Presently, a pilot project, initiated by the California Medical Association and directed by Westberg, is underway to determine the feasibility of reviewing all maternal and infant deaths in California (California Medical Association. Physicians to study causes of maternal and infant deaths [News release], 1979). The study, which entails a random sampling of 10% of all such deaths, may establish the feasibility of renewing statewide studies. The Special Interest Committee on Maternal Mortality of the American College of Obstetricians and Gynecologists (championed by Hofmeister, Ruppersberg, Rochat, and others and now chaired by Jewett) also is active in a program to accomplish these tasks (Rochat RW. Maternal mortality worksheet. Minutes of 1983-1984 meeting of the Special Interest Group in Maternal Mortality). Interested obstetricians are urged to file collected patient reports on a standard form that is being circulated. Although the form presently derives much valuable demographic data, it eventually should produce more clinical information also.

A general decrease in maternal mortality rates is an inadequate basis for considering that maternal mortality studies are no longer necessary or cost-effective. Maternal mortality study committees will continue to be a necessary effort as long as the conclusions of such reviews indicate that death was preventable because of substandard patient care, with too little being done, too late. Prospectively, the data accrued by these committees have the potential to contribute substantially to a nationwide study of the causes of obstetric mortality. Since our study population is small, our findings are not of great value as an individual effort. We report our methods and results to illustrate the simplicity of carrying out such a study and its usefulness to the local community. We are committed to continuing our efforts and encourage all states and territories to contribute their observations in a broad-based, cumulative maternal mortality series directed toward the eventual elimination of preventable maternal deaths.

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Discussion

DR. CLYDE V. VON DER AHE, Los Angeles, California. Dr. Fox is to be commended for bringing the subject of the revival of maternal mortality committees before this society. In the past 10 years, more than 200 formal papers on various subjects have been read before this society. However, not a single paper on this subject has been presented. It is timely indeed.

The author is quite right in saying that the original California maternal mortality committees were discontinued and financing was withheld in the late 1960s because the decreasing number of maternal deaths limited significantly the value of such statistical studies.

However, in the late 1970s the chairman of the California Medical Association Committee on Maternal, Perinatal and Child Care became concerned about the lack of valid mortality statistics. The fact was that maternal mortality rates were not dropping, although extensive federal and state perinatal programs were being developed.

In cooperation with the state department of health the California Medical Association developed a committee to study (1) all maternal deaths, (2) all out-of-hospital neonatal and fetal deaths, and (3) a random 10% sampling of in-hospital neonatal and fetal deaths. This is a gargantuan task.

Numerous difficulties have been encountered. Among these are (1) getting permission from the state Bureau of Vital Statistics, which is needed for access to the confidential portion of the fetal death certificate; (2) obtaining the consent of the surviving kin of the subject studied, as originally required by the state Committee on Protection of Human Subjects. Obtaining consent was expensive and time consuming. Finally, a waiver was obtained to allow access to hospital records without the consent of kin.

Other problems encountered by the committee had to do with the availability of death certificates. According to the California law, a death certificate is not available for 1 to 3 years after a death. It was also found that many abortions were being reported as fetal deaths. Cooperation of hospitals in allowing access to their records in cases of maternal deaths, was not optimal; when a case was transferred from one institution to another, the accompanying records were inadequate.

The committee also has identified 13 maternal deaths not previously recorded. As a result the California Medical Association is attempting to have the following change enacted in the death certificate, namely, insertion of a box to be checked if a woman was pregnant or delivered within 90 days preceding death.

The committee is reviewing maternal deaths for 1980, 1981, and 1982. A preliminary report in the spring of 1985 is anticipated (personal communication).

Are these committees really justified? Pearse[1] asks this question in an editorial entitled "Maternal Mortality Studies—Time to Stop?" He points out that in 1977 there were approximately 400 direct maternal deaths in the United States and approximately 75,000 fetal and neonatal deaths. He feels that the number of maternal deaths are small. They merit continued study but not at the intensity of former years or to the exclusion of perinatal mortality studies.

Hofmeister[2] points out that "mothers are still mortal." They still die of complications of pregnancy and parturition. Practically all studies implicate the triad of hemorrhage, infection, and toxemia as the leading causes of direct obstetric deaths. This has not changed in the past 20 years.

Practically all studies indicate that two thirds to three fourths of obstetric maternal deaths are preventable. In assessing responsibility, be it physician, patient, or hospital, physician responsibility ranks first. This is a grave indictment, carrying with it not only moral implications but also serious medicolegal problems.

It is to be remembered that committees do not treat patients. However, the information gathered by committees is not only helpful but very instructive. In that vein I propose the formation of a maternal mortality and perinatal mortality committee in each caucus of this society, with a report of the activities of such a committee to be presented to the members every 3 years.

Finally, I congratulate our essayist. There is little to quarrel with because his material is well organized and thoughtfully presented.

Referring to Table I, I should like to ask the author for the following information: (1) the number of maternal mortality meetings per year, (2) the average cost in dollars to prepare each case for committee presentation, and (3) the average time lapse from the maternal death until the case is ready for presentation.

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DR. JIMMIE WESTBERG, San Francisco, California. I am the committee chairman who is presently heading the California Medical Association program on maternal mortality and I would like to identify the person who started this project, Dr. Lester Hibbard. Two other members of this society are on the committee: Drs. Solon Barbis and Tom Moyers. Unfortunately, I cannot discuss our findings at this time. We have just entered the data in the computer, and the findings should be available in 2 to 3 months. However, 20% of the maternal deaths are missed if you look only at the death certificates. Our cost per case is somewhere between $450 and $500. Ectopic pregnancy, at 20% to 25%, is the largest cause of maternal death. About 5% to 10% of maternal deaths are due to accidents or homicides. We have coined a new term called SADS, which is the "sudden adult death syndrome," somewhat like SIDS, or sudden infant death syndrome, and which occurs in 4% or 5% of maternal deaths for which there are no findings on postmortem examination. Within the next 6 to 8 months we should have a paper ready with all of our findings.

DR. DONALD MINKLER, Berkeley, California. I want to congratulate Dr. Fox for reopening this question because it is quite clear we have not reached the irreducible minimum in maternal deaths. I would like to enter a plea to the committee to expand its horizon beyond the study on a case-by-case basis of individual risks of pregnancy to mothers. For example, in the area of infant mortality a study was done several years back by Morris et al.,[1] showing that about 27% of the decline in infant mortality in the United States between the years 1960 and 1975 could be attributed to changes in the age structure of the childbearing population, which is a reflection of greater access to and greater practice of family planning. The policy issues that affect maternal risks in this area in California include the 2 years of significant budget cuts by the state administration amounting to 9.5 million dollars each year in the budget of the Office of Family Planning. This affects services to the low-income population, which many studies have shown to bear disproportionately the burden of maternal as well as infant mortality. I am quite sure that a corresponding study of changes in the age/parity structure of the childbearing population will show equally the effect that delaying, spacing, or limiting births has on maternal risks and will encourage policy changes aimed at further reducing them.

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DR. FOX (Closing). I appreciate the supportive discussion, which is needed to propel more interest in widespread maternal mortality study committees. In answer to Dr. Von Der Ahe's questions concerning our county study committee, we average approximately two meetings per year depending upon the accumulation of cases. I am unable to give you the exact expense of our meeting, which in fact is borne by the county medical society, but it includes two mailings for each meeting of copied records and meeting notices. Also, the

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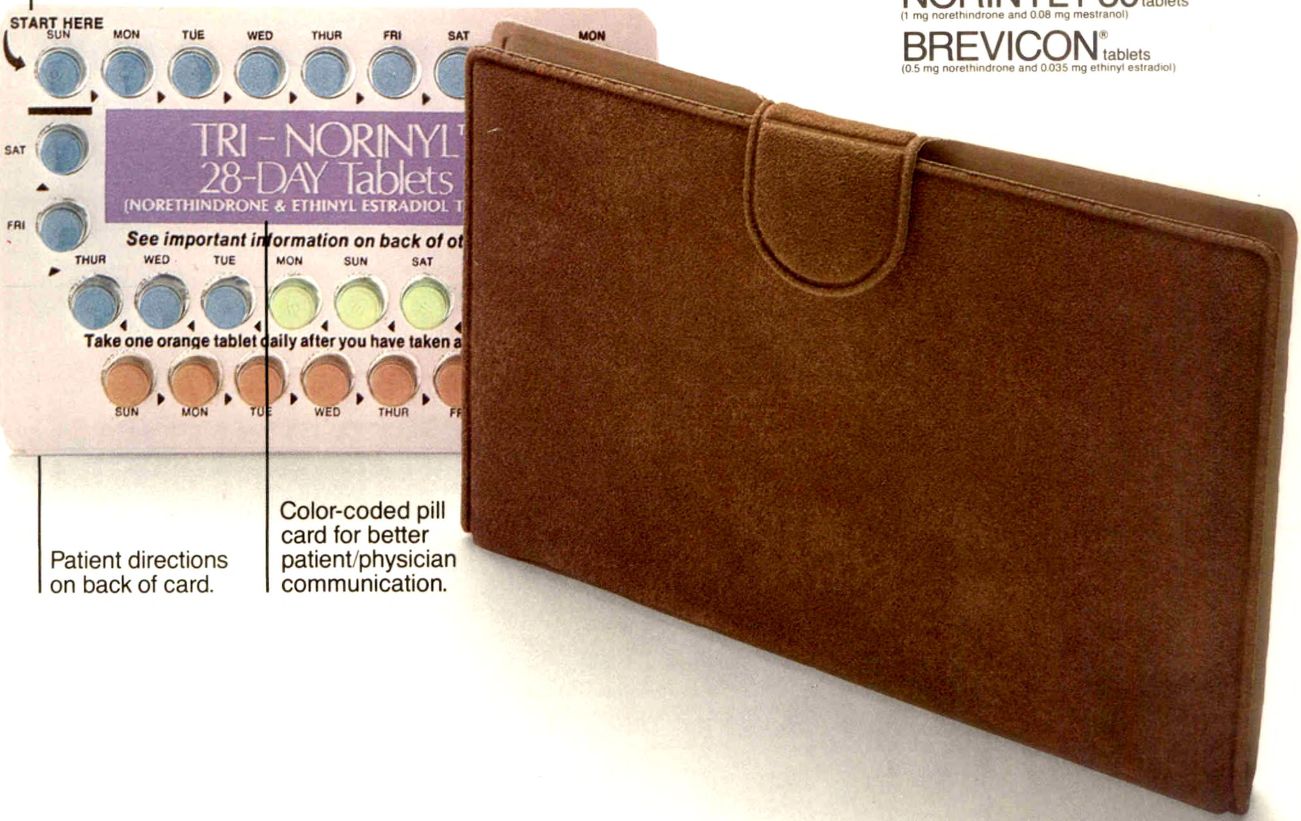
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1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with OC use is established. One study demonstrated an increased relative risk for fatal venous thromboembolism and several studies demonstrated it for non-fatal venous thromboembolism. They estimate that OC users are 4-11 times more likely than nonusers to develop these diseases without evident cause. One British study reported an excess death rate of 40% in OC users, most of which resulted from cardiovascular disease. Another British study showed a lower death rate in OC users than controls; an increase in cardiovascular deaths was seen but was not statistically significant. A U.S. prospective study failed to disclose increased mortality rates from cardiovascular disorders, but a subset analyzed as a retrospective, case-control study showed significant increases in venous thromboembolism. CEREBROVASCULAR DISORDERS. Two American studies demonstrated an increased relative risk for stroke not shown in prior British studies. In an American study of cerebrovascular disorders in women with and without predisposing causes, relative risk of hemorrhagic stroke was estimated as 2.0 times greater and thrombotic stroke as 4-9.5 times greater in users than nonusers. A British long-term, follow-up study reported in 1978 a highly significant association between OC use and stroke. Another study had suggested an association in 1974, but the number of cases was too small to estimate the risk. Subarachnoid hemorrhage has been shown to be increased by OC use in British and American studies. Smoking alone increases incidence of these accidents; smoking and pill use appear to increase risk more than either alone. MYOCARDIAL INFARCTION (MI). Increased relative risk of MI associated with OC use has been reported. One British study found that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing MI, regardless of OC use. OCs were an additional risk factor. In terms of relative risk, it has been estimated that nonsmoking OC users (smoking is considered a major predisposing condition to MI) are twice as likely to have a fatal MI as nonsmoking nonusers. OC users who are smokers have a 5-fold increased risk of fatal infarction compared to nonsmoking users, and a 10-12-fold increased risk compared to nonsmoking nonusers. The number of cigarettes smoked is important. In determining the importance of these relative risks, baseline rates for various age groups must be considered. (Estimates are based on British vital statistics which show acute MI death rates 2-3 times less than in the U.S. so U.S. death rates could be higher.) Importance of other predisposing conditions in determining relative and absolute risks has not been quantified; other synergistic actions may exist. RISK OF DOSE. Using data from several national adverse reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to estrogen dose in OCs. OCs with 0.1 mg or more of estrogen were associated with a higher risk of thromboembolism than those containing 0.05-0.08 mg but quantity of estrogen may not be the sole factor. This was supported by a U.S. study. A British study found a positive association between dose of progestogen or estrogen and certain thromboembolic conditions. Swedish authorities noted decreased reporting of thromboembolic episodes when higher estrogen preparations were no longer prescribed. Careful epidemiological studies to determine degree of thromboembolic disease risk associated with progestogen-only OCs have not been done. Thromboembolic disease has been reported in women using these products, and they should not be considered free of excess risk. PERSISTENCE OF RISK. Two studies have suggested an increased risk may persist for 6 years after discontinuation of OC use for cerebrovascular disease and 9 years for MI; another study suggested persistence of risk for subarachnoid hemorrhage. ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES. A large British prospective study estimated mortality rate per 100,000 women per year from circulatory system diseases for OC users and nonusers according to age, smoking habits, and duration of use. The overall annual excess death rate for OC users was estimated to be 20/100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000). Risk is concentrated in long-term users and in smokers, and may persist after OC discontinuation. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all occurred in women 35 or older. An update provided the following rates: ages 15-34—1/6700 for nonsmokers and 1/2000 for smokers; ages 45 and over—1/2500 for nonsmokers and 1/500 for smokers. Risk appeared to increase with parity, but not with duration of use. Until more women under 35 with continuous use for 5 or more years are available, it is not possible to assess relative risk for this age group. Data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates include combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease for OCs) plus risk attributable to pregnancy or abortion if the method fails (which varies with the effectiveness of the contraceptive method). Data are shown in Table 1 below. The study concluded that mortality associated with all contraceptive methods is below that of childbirth, except for OCs in women over 40 who smoke. (Rates given for pill only/smokers for each age are for smokers as a class. For "heavy" smokers (more than 15 cigarettes a day), rates would be about double; for "light" smokers (less than 15), about half.) The lowest mortality is with the condom or diaphragm backed up by early abortion. The study also concluded that OC users who smoke, especially over 30, have greater mortality risk than OC users who do not smoke.

Table 1. *Risk of thromboembolic and thrombotic disease associated with OCs increases with age after 30 and, for MI, is further increased by hypertension, hyperlipidemias, obesity, diabetes, or history of preeclamptic toxemia, and especially by smoking. The following chart gives a gross estimate of risk of death from circulatory disorders associated with OC use.*

SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS—RISK ASSOCIATED WITH USE OF OCs

Age	Below 30	30-39	40+
Heavy smokers	C	B	A
Light smokers	D	C	B
Nonsmokers (no predisposing conditions)	D	C,D	C
Nonsmokers (other predisposing conditions)	C	C,B	B,A

A—Use associated with very high risk.
B—Use associated with high risk.
C—Use associated with moderate risk.
D—Use associated with low risk.

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, discontinue OC immediately. A 4-6 fold increased risk of post-surgery thromboembolic complications has been reported in OC users. If feasible, discontinue OCs at least 4 weeks before surgery associated with increased risk of thromboembolism or prolonged immobilization. Before resuming OC after major surgery or bedrest, balance risks of post-surgery thromboembolic complications with contraceptive needs. Data suggest varicose veins substantially increase risk of superficial venous thrombosis of the leg, the risk depending on severity of the varicosities. 2. *Ocular Lesions:* Neuro-ocular lesions such as optic neuritis or retinal thrombosis have been associated with OC use. Discontinue OC if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions; and institute appropriate diagnostic and therapeutic measures. 3. *Carcinoma:* Long-term continuous administration of natural or synthetic estrogen in certain animals increases certain tumors, benign or malignant, such as breast, cervix, vagina, uterus, ovary, pituitary and liver. Certain synthetic progestogens, none currently in OCs, increase the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studies reported an increased relative risk (3.1-13.9 times) associating endometrial carcinoma with prolonged use of estrogens in postmenopausal women. One publication reported the first 30 cases submitted to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OCs. Of the adenocarcinomas found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding when OCs were first given, polycystic ovaries), nearly all occurred in women who had used sequential OCs, which are no longer marketed. No statistical association has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only OCs, although individual cases have been reported. Studies have shown no increased risk of breast cancer to OC or estrogen users. One study found no overall increased risk of breast cancer in OC users but a greater risk was suggested for OC users with documented benign breast disease and for long-term (2-4 years) users. Another study found a history of breast cancer among grandmothers or aunts was significantly more frequent among breast cancer patients who had used an OC continuously for one or more years than among nonusers with breast cancer. One other study indicated an increasing risk of breast cancer in women taking menopausal estrogens, which increased with duration of follow-up. One author suggests that extended (over 6 years) OC use prior to first full term pregnancy was associated with a significant relative risk of breast cancer. A reduced occurrence of benign breast tumors in OC users has been well documented. One study reported malignant melanoma more frequently in OC users than controls and suggests an increased incidence of urinary tract and thyroid cancers. A prospective study of women with cervical dysplasia found an increase in severity and conversion to cancer *in situ* in OC users compared with nonusers. This became statistically significant after 3-4 years of use. Nonreversal of dysplasia within the first 6 months of pill use was suggested to predict progression after prolonged exposure. One study disclosed an increased risk of cancer of the cervix (largely carcinoma *in situ*) in OC users under 40, particularly those who had used OCs over 4 years. There have been other reports of microglandular hyperplasia of the cervix in OC users. One study reported an association between OC use and endocervical adenocarcinoma. In summary, there is no confirmed evidence from human studies of increased risk of cancer associated with OCs. Close clinical surveillance of all OC users is, nevertheless, essential. In all cases of undiagnosised persistent or recurrent abnormal vaginal bleeding, take appropriate diagnostic measures to rule out malignancy. Monitor OC users with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms with particular care. 4. *Liver Tumors:* Sudden severe abdominal pain or shock may be due to rupture and hemorrhage of a liver tumor. There have been reports associating benign or malignant liver tumors with short-term and long-term OC use. One study reported use of OC's with high hormonal potency and age over 30 may further increase risk of hepatocellular adenoma. Two studies relate risk with duration of use, risk being much greater after 4 or more years of use. Long-term OC users have an estimated annual incidence of hepatocellular adenoma of 3-4/100,000. Although an uncommon lesion, it should be considered in women presenting with an "acute abdomen." The tumor may cause serious or fatal hemorrhage. Patients with liver tumors have demonstrated variable clinical features which may make preoperative diagnosis difficult. Some cases presented because of right upper quadrant masses, while most had signs and symptoms of acute intraperitoneal hemorrhage. Routine radiological and laboratory studies may not be helpful. Liver scans may show a focal defect. Hepatic arteriography may be useful in diagnosing primary liver neoplasm. 5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring:* Use of female sex hormones—estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. Females exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be of the order of 1/1000 exposures or less. Although there is no evidence that OCs further enhance the risk of developing this type of malignancy, such OC users should be monitored with particular care. A high percentage of women exposed to diethylstilbestrol (30-90%) have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are a precursor of vaginal malignancy. Male children so exposed may develop urogenital tract abnormalities. Although similar data are not available on other estrogens, it cannot be presumed that they would not induce similar changes. Increased risk of congenital anomalies, including heart and limb defects, has been reported following use of sex hormones, including OCs, in pregnancy. One case-control study estimated a 4.7-fold increased relative risk of limb-reduction defects in infants exposed *in utero* to sex hormones (OCs, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some exposures involved only a few days of treatment. Data suggest risk of limb-reduction defects in exposed fetuses is somewhat less than 1/1000 live births. In a large prospective study, cardiovascular defects in children born to women who received female hormones, including OCs, during early pregnancy occurred at 18.2/1000 births, compared to 7.8/1000 for children not so exposed *in utero*. These results are statistically significant. A Welsh study found a statistically significant excess of neural tube defects among offspring of prior OC users (within 3 months) than among controls. The incidence of twin births may be increased for women who conceive shortly after discontinuing OC use. In the past, female sex hormones were used during pregnancy in an attempt to treat threatened or habitual abortion. There is evidence that estrogens are ineffective, and there is no evidence from well controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OCs. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OCs is unknown. If the patient has not adhered to the prescribed schedule, consider possible pregnancy at the first missed period (or 45 days from the last menstrual period if progestogen-only OCs are used) and discontinue OC use until pregnancy has been ruled out. For any patient who has missed two consecutive periods, rule out pregnancy before continuing the OC. If pregnancy is confirmed, tell the patient about potential risks to the fetus and discuss advisability of continuing the pregnancy. Women who discontinue OCs to become pregnant should use an alternate form of contraception for a period of time before attempting to conceive. A 3-month period is supported by a study suggesting increased frequency of neural tube defects in women impregnated during the first 3 months after cessation of OC use. Do not use progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding as a pregnancy test. 6. *Gall Bladder Disease:* Studies report increased risk of gall bladder disease in OC or estrogen users. In one study, an increased risk appeared after 2 years of use and doubled after 4-5 years. In another study, an increased risk was apparent between 6 and 12 months. 7. *Carbohydrate and Lipid Metabolic Effects:* Because a decrease in glucose tolerance has been observed in a significant percentage of patients on OCs, prediabetic and diabetic OC users should be carefully observed. An increase in triglycerides and total phospholipids has been observed in OC users but its clinical significance is unknown. 8. *Elevated Blood Pressure:* An increase in blood pressure has been reported with OC use. Hypertension may occur within a few months of beginning OCs. In the first year of use, incidence of hypertension may be no higher in OC users than in nonusers. Incidence in users increases with exposure and in the fifth year of use is 2.5-3 times that in the first year. Age is strongly correlated with hypertension in OC users. Women with a history of elevated blood pressure (hypertension), preexisting renal disease, history of toxemia or elevated blood pressure during pregnancy, familial tendency to hypertension or its consequences, or history of excessive weight gain or fluid retention during the menstrual cycle may be more likely to develop elevated blood pressure when given OCs and should be monitored closely. Even though elevated blood pressure may remain within the "normal" range, closely watch elevations, particularly for women with other risk factors for cardiovascular disease or stroke. High blood pressure may or may not persist after OC discontinuation. 9. *Headache:* Discontinue OC and evaluate the cause of onset or exacerbation of migraine or development of a new pattern of headache which is recurrent, persistent, or severe. 10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and missed menses often make users discontinue OCs. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, consider nonfunctional causes. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, use adequate diagnostic measures to rule out pregnancy or malignancy. If pathology has been excluded, time or another formulation may solve the problem. While potentially useful in minimizing menstrual irregularity, change to an OC with a higher estrogen content only if necessary since this may increase risk of thromboembolic disease. Women with a history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may tend to remain anovulatory or to become amenorrheic after OC discontinuation. Women with these preexisting problems should be advised of this and encouraged to use other contraceptive methods. Post-use anovulation, possibly prolonged, may occur in women without previous irregularities. A higher incidence of galactorrhea and of pituitary tumors (e.g., adenomas) has been associated with amenorrhea in former users compared with nonusers. One study reported a 16-fold increased incidence of pituitary prolactin-secreting tumors among patients with postpill amenorrhea when galactorrhea was present. 11. *Infertility:* There is evidence of impairment of fertility in women discontinuing OCs in comparison with other contraceptive methods, which appears to be independent of duration of use. While impairment diminishes with time, there is an appreciable difference in results in nulliparous women for OC and other groups 30 months after discontinuation of birth control. For parous women the difference is not apparent 30 months after cessation of contraception. 12. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in OC failures. In progestogen-only OC failures, the ratio of ectopic to intrauterine pregnancies is higher than in nonusers, since the drugs are more effective in preventing intrauterine than ectopic pregnancies. 13. *Breast Feeding:* OCs in the postpartum period may interfere with lactation by decreasing quantity and quality of breast milk. A small fraction of OC hormonal agents has been identified in milk of mothers receiving OCs. Effects, if any, on the breast-fed child have not been determined. If feasible, defer OC use until the infant has been weaned. **Precautions** *GENERAL* 1. Take a complete medical and family history before starting OCs. Pretreatment and periodic physical exams should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant lab tests. As a general rule, OCs should not be prescribed for longer than 1 year without another physical. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may enlarge. 3. Observe patients with a history of psychic depression and discontinue OCs if depression recurs to a serious degree. Patients becoming significantly depressed while taking OCs should stop the OC and use an alternate method of contraception to determine whether the symptom is drug related. 4. OCs may cause some fluid retention. Prescribe with caution, and only with careful monitoring, in patients with conditions that might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma or cardiac, hepatic or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while using OCs. Discontinue OC if jaundice develops. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. OC users may have disturbances in normal tryptophan metabolism that may result in a relative pyridoxine deficiency. The clinical significance is unknown. 8. Serum folate levels may be depressed by OC use. Since the pregnant woman is predisposed to folate deficiency and incidence of folate deficiency increases with increasing gestation, if a woman becomes pregnant shortly after stopping OCs, she may have a greater chance of developing folate deficiency and related complications. 9. Advise the pathologist of OC use when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing OCs. For example: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnandiol excretion. e. Reduced response to metyrapone test. f. Increased phospholipids and triglycerides. g. Temporarily decreased glucose tolerance. 11. Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist and temporary or permanent cessation of wear considered. DRUG INTERACTIONS. OCs may be less effective and there may be increased breakthrough bleeding because of interactions with rifampin, isoniazid, ampicillin, tetracycline, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, analgesics, tranquilizers, anti migraine preparations, and antihistamines. OCs may alter effectiveness of such other drugs as oral anticoagulants, anticonvulsants, tricyclic anti depressants, antihypertensive agents (e.g., guanethidine), vitamins, hypoglycemic agents, tranquilizers, hypnotic preparations, and theophylline. *CARCINOGENESIS* See Warnings. *PREGNANCY* Pregnancy category X. See Contraindications and Warnings. *NURSING MOTHERS* See Contraindications and Warnings. **Adverse Reactions** An increased risk of the following serious adverse reactions has been associated with OC use (see Warnings): thrombophlebitis, thrombosis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, mesenteric thrombosis, liver tumors, cerebral hemorrhage, hypertension, gall bladder disease, congenital anomalies, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, Raynaud's disease arterial thromboembolism. The following adverse reactions have been reported in OC users and are believed to be drug related: bleeding irregularities (breakthrough bleeding, spotting, missed menses during treatment, amenorrhea after treatment), gastrointestinal symptoms, (nausea, vomiting, bloating, abdominal cramps), dysmenorrhea, infertility after discontinuance of treatment, edema, chloasma or melasma which may persist after drug is discontinued, breast changes (tenderness, enlargement, and secretion), intolerance to contact lenses, change in corneal curvature (steepening), change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, prolactin-secreting pituitary tumors, chilblains. The following adverse reactions have been reported in OC users and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness hirsutism, loss of hair, erythema multiforme, erythema nodosum, hermorrhagic eruption, vaginitis, porpyhria, impaired renal function, malignant nephrosclerosis (hemolytic uremic syndrome). **Information for the Patient** (See Patient Package Insert)

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Lymphatic spread in carcinoma of the vulva

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A study of 153 patients with squamous cell carcinoma of the vulva is reviewed. Regional node metastases were present in 20%, and lymphatic spread proved the single most significant prognostic factor in this disease. Recurrent carcinoma developed in 47% of cases with nodal metastases. Lymph node metastases were directly related to stage of disease, tumor differentiation, lesion size, and depth of invasion. Sixty percent of nodal disease was not suspected by clinical examination. No patient developing recurrent disease after identification of positive nodes survived the disease. Surgical staging based only upon size of lesion and presence of nodal metastases appears to offer a clearer prognostic profile than conventional clinical staging. The pattern and frequency of nodal spread suggest that in selected instances modifications of the standard surgical treatment of vulvar cancer may be appropriate. (AM J OBSTET GYNECOL 1985;152:387-94.)

Key words: Carcinoma, vulva, lymphatic spread

Over the past few years considerable interest has been directed toward identifying subgroups of patients with invasive carcinoma of the vulva for whom treatment patterns of a more conservative nature than the traditional radical vulvectomy and bilateral groin dissection might be employed. The risks of the radical procedure among patients in the age range commonly identified with vulvar cancer together with the substantial morbidity and deformity resulting from the procedure provide an understandable stimulus for such speculation. Various modifications have been proposed, ranging from wide local excision to radical vulvectomy and unilateral lymphadenectomy.[1-5] There has been a general agreement that such modifications should be restricted to localized and well-lateralized lesions that fall into the Stage I category. The criteria for further selection have been inconsistent and include depth of invasion, histologic grade, presence or absence of palpable nodes, and vascular invasion. No uniformly acceptable or agreed-upon criteria have emerged, and it would appear that additional data must accumulate to afford statistical substance to such proposals. It is particularly important to define those precise variables that will permit an accurate definition of the subgroups in which treatment modifications may be safely employed.

In a previous review of a group of 38 patients with Stage I disease, criteria have been defined, applicable to 23 of the 38, whereby it was felt that the lesion could be regarded as microinvasive and safely treated as carcinoma in situ with wide local excision as the initial procedure.[1] Many patients with early Stage I disease, however, fail to meet these strict criteria but present with lesions for which less than the traditional radical operation may be appropriate. This report is a further effort to define the risk factors that would apply in such instances.

Material and methods

Medical records of 179 patients treated for carcinoma of the vulva at the University of Washington Hospitals through 1982 were available for review. Thirteen patients were diagnosed as having melanoma, eight as having carcinoma of Bartholin's gland, five as having verrucous carcinoma, and 153 as having squamous carcinoma. The present review is limited to those patients with squamous carcinoma.

All records were individually reviewed by one author. Stage of disease was assigned on the basis of current criteria adopted by the International Federation of Gynecology and Obstetrics. Twenty-eight separate variables were coded for each patient and entered into a data file prepared for a TRS-80 Model II microcomputer. Retrieval of the data was carried out by a computer-programmed analysis of variables; χ^2 and probability values were derived from statistical programs designed for the computer.

Age. The mean age of all patients was 65 years. The youngest patient was 35 years of age and the oldest 86. About 14% of patients were under the age of 50, and 3.3% were below the age of 40.

Stage of disease. The stages of disease were as follows: Stage I, 55 patients; Stage II, 61; Stage III, 31; Stage IV, 6. When stage of disease was related to three arbitrary time periods encompassed within the study,

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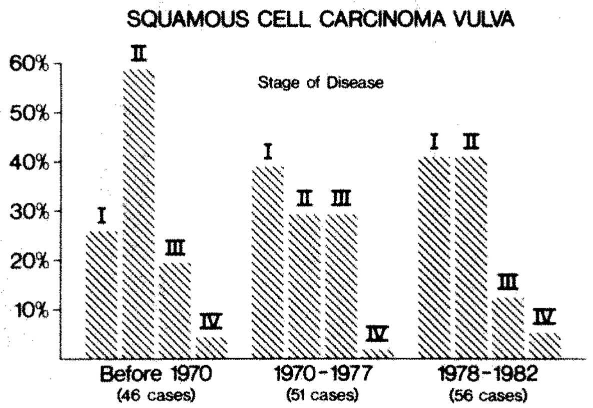

Fig. 1. Stage of disease by time periods encompassed within the study.

Table I. Stage of disease and nodal metastases

Stage	No. of patients	Positive nodes	
		n	%
I	55	3	5.5
II	61	13	21.5
III	31	12	38.7
IV	6	2	33.3
	153	30	19.6

there was no statistical difference in the assignment of stage within the time periods represented (Fig. 1). An increasing number of Stage I cases were seen after 1970 in comparison with earlier years, but even this difference failed to reach the usually accepted levels of statistical significance ($p = 0.086$).

Location. One hundred twenty-three of the 153 cases were described as occurring on the labia majora or minora. Sixteen of the lesions occurred on the perineum and six on the clitoris; only eight lesions were described as being multifocal or diffuse in origin.

Treatment. A variety of treatment patterns were employed over the years of this review. Twelve patients were treated by radical vulvectomy alone, 83 by radical vulvectomy and bilateral groin dissection, 32 by radical vulvectomy, bilateral groin and pelvic lymphadenectomy, and six by some form of exenteration. The remaining patients had lesser procedures carried out. Twenty-seven patients had some form of radiation therapy employed in addition to the surgery.

Results

The primary purpose of this review was to study patterns and frequency of lymph node metastases. Eighty percent of the patients had treatment that included some form of lymph node dissection. Thirty patients had no lymphadenectomy performed, 93 had a lymphadenectomy with negative nodes, and 30 had demonstrable regional node metastases. Nineteen had ipsilateral groin metastases, five had bilateral groin metastases, and six patients had disease that spread to the pelvic lymph nodes. There were no instances of bilateral pelvic node metastases and no instances of contralateral node involvement in the absence of positive ipsilateral nodes. No patient had pelvic node involvement in the absence of ipsilateral groin node metastases. Nine patients had only one positive node, seven had two positive nodes, four had three positive nodes, and five had four positive nodes. Five patients had five or more positive nodes. The average patient had 20 to 30 nodes removed and examined. The majority of patients had only microscopic involvement of the nodes. Ten had >50% nodal replacement or extranodal extension. Presence or absence of regional node spread proved the most convincing and constant determinant for predicting subsequent recurrence or survival. Among the 30 patients in whom positive nodes were encountered, there was a 46.7% incidence of recurrent disease, and all such patients who developed recurrence in the presence of positive nodes are now dead of the disease. Among the remaining 123 patients the recurrence rate was 8.1%.

Table II. Predictive accuracy of clinical examination

Assessment of nodes	*No. of patients*	%
Clinically "negative" nodes	107	
Lymphadenectomy and negative nodes	89	83.2
Regional node metastases	18	16.8
Clinically "suspicious" nodes	12	
Lymphadenectomy and negative nodes	4	33.3
Regional node metastases	8	66.7
Clinically "positive" nodes	4	
Lymphadenectomy and negative nodes	0	0.0
Regional node metastases	4	100.0
False negative results among 30 patients	18	60.0

Table III. Lesion size and incidence of nodal metastases

	No. of patients	%
Lesion size < 2 cm	39	
Negative nodes	34	87.2
Positive nodes	5	12.8
Lesion size > 2 cm	83	
Negative nodes	58	
Positive nodes	25	30.1

$p = 0.0319$.

The frequency of nodal metastases bore a linear correlation with stage of disease (Table I). The criteria for clinical staging included a clinical assessment of the groin nodes. Our predictive accuracy in this respect is summarized in Table II. In 83% of instances the clinical impression of negative nodes was correct. Conversely,

Table IV. Lesion size and recurrent disease in 92 cases of squamous carcinoma with negative nodes

	No. of patients	Recurrences	
		n	%
Lesion size < 2 cm	34	2	5.8
Lesion size > 2 cm	58	6	10.3

p = 0.821.

Table V. Tumor differentiation and nodal spread

Histology	No. of patients	Positive nodes	
		n	%
Well differentiated	53	7	13.2
Moderately differentiated	51	18	19.6
Poorly differentiated	29	18	34.5

p = 0.07.

Table VI. Prior dystrophy and stage of disease

Stage	Prior dystrophy		No prior dystrophy	
	n	%	n	%
I	23	56.1	32	28.6
II	12	29.3	49	43.7
III	5	12.2	26	23.2
IV	1	2.4	5	4.5
Total	41		112	

p = 0.079.

Table VII. Depth of invasion and positive nodes

Depth of invasion (mm)	No. of patients	Positive nodes	
		n	%
<5	36	2	5.56
>5	117	28	23.9

p = 0.0116.

among the 30 patients with regional node metastases 18, or 50%, were clinically regarded as having negative nodes.

Lesion size alone, exclusive of all other criteria, serves as a statistically significant issue in predicting nodal disease (Table III). The probability of occurrence of positive nodes rises from 12.8% to 30.1% in lesions that exceed 2 cm in maximal diameter. In terms of recurrent disease, however, lesion size appears to be less significant than regional node involvement (Table IV). Among 92 patients with negative nodes disease recurred for 5.8% if the lesion was <2 cm in diameter and for 10.3% if the lesion exceeded that size. The difference is not statistically significant.

Lesions were histologically designated as "well differentiated," "moderately differentiated," or "poorly differentiated" in 133 patients. In 18 patients no histologic description was available, and in two other patients a characteristic "spray" pattern was observed. The probability of nodal involvement increases in a linear fashion with histologic grade of disease although the pattern would appear to fall just short of statistical significance (Table V).

In a review of the patient records, 27% of cases yielded a history of prior or concomitant vulvar dystrophy. Such prior or current dystrophy might be expected to be reflected in earlier disease either through earlier diagnosis or within the context of a less aggressive lesion. There was a definite shift toward earlier stages of disease among patients with prior dystrophy although the contrast again did not reach the level of statistical reliability (Table VI).

Depth of invasion was measured or calculated from the surface of the lesion. Among the 36 patients in whom depth of invasion was <5 mm, the incidence of nodal metastases was 5.56% (Table VII). Among the remaining 117 patients the incidence of nodal spread was 23.9%. Among the 25 patients with Stage I carcinoma in which depth of invasion was <5 mm, only one (4%) proved to have nodal spread.

Vascular or lymphatic space invasion was described in 10 instances. Six of these patients proved to have positive nodes in the surgical specimen, but four of the six had Stage III or IV disease. All patients with positive nodes are dead, but two died of unrelated causes. The significance of such vascular or lymphatic space invasion remains uncertain. Four additional patients had perineural invasion without vascular or lymphatic space involvement. Three of these patients are without evidence of disease, and the remaining patient had a poorly differentiated tumor with four positive node metastases.

Recurrent carcinoma. Twenty-four patients (15.7%) are known to have developed recurrent carcinoma. Two are alive without evidence of disease following secondary treatment. Twenty-one are dead of disease, and one patient died of other causes. Fourteen of the recurrences were associated with positive nodes (58.3%), and all patients who had a recurrence after positive node involvement are dead of disease. Seven of the fourteen cases with nodal spread were clinically considered to have negative nodes at the time of initial treatment. Twelve of the 14 patients with positive nodes and recurrent carcinoma had two or more positive nodes at the time of surgery. In the context of original surgical findings, the risk of recurrence with a single

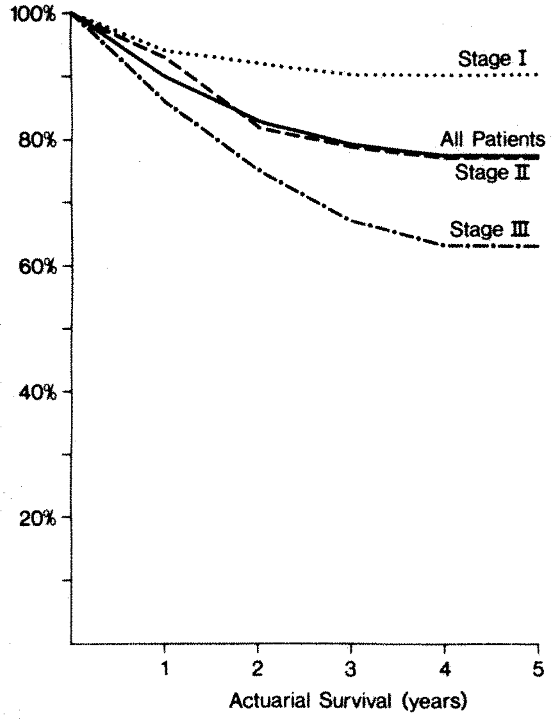

Fig. 2. Actuarial survival of all cases of squamous carcinoma of the vulva.

Table VIII. Relationship of stage in recurrent carcinoma

Stage	*No. of patients*	*Recurrence*	
		n	*%*
I	55	3	5.5
II	61	12	19.7
III	31	8	25.8
Total	147		

$p = 0.0101$.

Table IX. Relationship of stage in recurrent carcinoma when patients with positive nodes are excluded

Stage	*No. of patients*	*Recurrence*	
		n	*%*
I	52	2	3.85
II	48	6	12.50
III	23	6	26.10

$p = 0.0189$.

Table X. Profile of recurrent carcinoma in patients who initially had nodal metastases

	Negative nodes	*Positive nodes*
Vulva	8	4
Groin	1	3
Pelvis	0	2
Distant	1	4
Unknown	0	1

node involved is 22.2%. If two or more nodes are involved, the risk of recurrence rises to 62.1%.

Of the five patients with lesion size of <2 cm associated with positive nodes, only one developed recurrent disease. This patient demonstrated a "spray" pattern of invasion on the initial histology.

Radiation therapy did not appear to be of significant benefit as adjuvant treatment following the surgical procedure. Of 12 patients so treated only one is alive without evidence of disease.

The incidence of recurrence was related to the stage of disease (Table VIII). Even when patients with known nodal metastases were excluded, there was a linear risk relationship with advancing stages (Table IX). Lesion size, as an independent variable, implies an increased risk of recurrence. Twenty-one percent of patients with a lesion >2 cm developed recurrence in contrast to a 5.8% incidence of recurrence if the lesion was <2 cm in diameter ($p = 0.0128$). Lesion size >2 cm carries an increased relative risk of 3.6 for recurrent disease.

The profile of recurrent disease was distinctly different for those patients who initially had metastatic disease in the lymph nodes (Table X). Ninety percent of recurrences in patients with negative nodes developed on the vulva or (in one instance) in the groin. Among patients with known nodal disease only 50% of recurrences were initially detected on the vulva or in the groin. In 80% of patients with a recurrence in the absence of node metastases, the recurrence developed on the vulva. In only 29% of those with nodal metastases was the recurrence detected on the vulva.

Although the clinical examination that serves as a framework for conventional staging appears to provide a valid index for the prediction of regional node metastases and for the probability of recurrent disease, it is apparent that information derived from surgical staging might even better define the prognostic outlook. With use of only two measurements of disease, lesion size and regional node involvement, a predictive model for recurrence might be designed that carried greater significance (Table XI). Within this model the risk of recurrence varies from 5.88% among patients with a small lesion and negative nodes to 60% among patients with a lesion size >2 cm associated with positive nodes.

Current status. One hundred three patients are currently without evidence of disease. Twenty-six have died of carcinoma and 13 have died of other causes. Eleven patients have been lost to follow-up.

Survival. Five-year survival was calculated by the actuarial or life table method.[2] Calculations were obtained for the entire patient population and by stage of disease

Table XI. Squamous carcinoma of the vulva and probability of recurrence

Lesion size (cm)	*Groin nodes*	*Frequency*	*%*
<2	Negative	2/34	5.88
>2	Negative	6/58	10.34
<2	Positive	1/5	20.00
>2	Positive	15/25	60.00

(Fig. 2). Survival of the entire population was 76.87%, approximately the same as that for patients with Stage II disease (76.5%). Survival in Stage I patients was 90.24% and for Stage III 62.61%. There were too few Stage IV patients to permit statistically valid calculations.

Comment

Information derived from this study would appear to support the concept that there is a population of patients with Stage I carcinoma of the vulva at sufficiently low risk for lymphatic spread or recurrence for whom a less aggressive pattern of treatment than the traditional radical vulvectomy and bilateral groin dissection should be appropriate. Several authors have expressed this conviction.[3-6] Others have argued against any modification of the traditional approach.[7] When a surgical approach has achieved a success rate as favorable as that which has been reached with this disease, one should indeed be cautious about suggesting any modification in the existing treatment. Despite improved operative techniques and postoperative measures, however, it has been pointed out that our control of vulvar carcinoma has not improved with this traditional approach over the past 30 years.[8] One might reasonably suggest that our efforts should be more aggressive with advanced disease, and correspondingly there may be room for a less aggressive approach with early lesions.

It has been suggested that the International Federation of Gynecology and Obstetrics staging of vulvar carcinoma, dependent to such a large degree on the clinical suspicion of involved regional nodes, should be supplanted by a surgical staging.[9] Certainly the failure to suspect such metastatic spread in 60% of instances would support this argument. Some authors have argued that a dividing line of 3 cm between early and advanced lesions has more significance than the conventional 2 cm diameter.[5, 9] Others have found no difference when the 3 cm measurement has been substituted.[10] It would seem appropriate to adhere to the 2 cm limits as long as the international staging includes it and convincing evidence of the superiority of a substitute figure is lacking. Iversen[11] has pointed out that substituting a surgical staging procedure would eliminate comments on fixed or ulcerated regional nodes which unquestionably impact upon the frequency of recurrence and survival. The staging system adopted by the International Federation of Gynecology and Obstetrics has been carefully assessed and found to be applicable clinically and valid.[12] The results of the present study would appear to confirm this impression. This staging system does permit recognition of histologic involvement of the regional nodes by a + or − symbol. It is unfortunate that this refinement is seldom included in literature defining the populations of this disease by clinical stage.

Lesion size,[8, 10, 13, 14] depth of invasion,[10, 14] histologic differentiation,[14, 15] and vascular, lymphatic or perineural invasion[3, 4, 10] have all been advanced as significant factors in predicting involvement of the regional nodes. Vascular or lymphatic permeation was described infrequently in this series of cases and, when present, was usually associated with large lesions as well as nodal spread. Perineural invasion, by contrast, appeared to have little significance. A more systematic and prospective search for such involvement, however, might well have provided a more definitive answer.

In attempting to develop criteria for a more conservative approach to early disease, it is essential to recognize that there are two subgroups that must be considered and separately defined. There are many early cases of vulvar cancer that may be appropriately designated as "microinvasive," in which the risk of metastatic spread is negligible and the treatment may involve a surgical approach similar or identical to that for carcinoma in situ. This population must be excluded in calculating the risk of metastatic spread in the remaining cases under consideration for conservative treatments. In this study the risk of nodal metastases in Stage I vulvar carcinoma, excluding those patients who might qualify as "microinvasive," would then approach 10%. DiSaia et al.[6] have defined a group of patients with squamous carcinoma in which the diameter of the primary lesion does not exceed 1 cm and the depth of invasion is <5 mm. They have proposed that such patients may be treated by wide local excision, providing that sampling of the superficial inguinal nodes proves negative by frozen section. Unlike the parallel problem faced with carcinoma of the cervix some years ago, the advantages of such a conservative approach in terms of morbidity and cosmetic results are indeed very substantial. With occasional exception,[7] most authors have found that contralateral node involvement in the absence of ipsilateral metastases is rarely observed.[1, 5, 13, 16] It has not occurred in this series. Most vulvar carcinoma presents as a well-localized lesion. Eighty percent of the cases in this report were localized to the labia majora or minora. In recognition of the risk factors represented in Stage I disease, it would seem reasonable to suggest now that all Stage I carcinomas of the vulva presenting as well lateralized lesions and with favorable histology could be approached initially by wide local excision and ipsilateral groin dissection. The 20% of patients who prove to have ipsilateral node metastases would, of course, require more extensive surgical resection.

Local recurrence or vulvar reoccurrence is, however, a problem that demands increased attention. The high mortality rate with any pattern of recurrence is alarming, and 42% of our recurrences developed in patients with negative nodes. The problem is primarily encountered in patients with advanced disease and large local lesions. It is quite uncommon in Stage I disease and usually associated with high-grade histology. We have seen only one exception to this observation, and that patient developed local recurrence after an interval of more than 5 years, suggesting that it may have represented reoccurrence rather than recurrent carcinoma.

Radical vulvectomy in continuity with bilateral groin dissection has proved an effective and successful treatment for carcinoma of the vulva. The sequelae in terms of morbidity and deformity are substantial but acceptable if no lesser procedure will achieve the same result in terms of disease control. Experience and numbers of cases reported, however, now suggest that modifications of the traditional approach are reasonable in early disease and that perhaps more extensive procedures such as exenteration or combined modalities of therapy should be considered in advanced disease. Today we should be willing to concede that a single rigid surgical approach to all vulvar carcinoma may not be in the best interest of the patient.

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Discussion

DR. WILLIAM J. SPANOS, Redlands, California. Dr. Figge has presented a retrospective study of 153 squamous cell carcinomas of the vulva treated at the University of Washington hospitals. The records were reviewed, and 28 separate variables were analyzed with the use of a microcomputer. The stated purpose of this review was to study patterns and frequency of lymph node metastases.

After analysis of the variables programmed and reorganized with the microcomputer, the authors identified lesion size, depth of invasion, and histologic grading as useful in determining in which patients a more conservative approach than a traditional radical vulvectomy and bilateral lymphadenectomy might be appropriate. According to the evaluation of these criteria, Stage I lesions had 5.5% positive lymph nodes, lesions of <2 cm had 12.8% positive lymph nodes, well-differentiated lesions had 13.2% positive lymph nodes, and lesions with depth of invasion of less than 5 mm had 5.56% positive nodes. According to the management proposed by the authors, all of these patients would have had additional surgery because of positive ipsilateral nodes.

Table IV indicates that there was a 5.8% recurrence of disease with a lesion <2 cm in size with negative nodes. In this series in 80% of the patients with negative nodes in whom the disease recurred, the lesion was in the vulva area. This high percentage of recurrences in the vulva in lesions with negative nodes is compatible with the known rich lymphatic supply of the vulva area both in the involved side and to the contralateral vulvar tissues.

At the Sixth World Congress of International Society for the Study of Vulvar Disease[1] the task force on microinvasive squamous cell carcinoma of the vulva evaluated diameter of the lesion and depth of invasion of ≤ 1 mm. In their report there were seven patients with lesion size of <0.5 cm and no lymph node metastases. There were two recurrences in these seven patients. Also, in 88 cases with a maximum invasion of 1 mm and no lymph node metastases there were eight patients with recurrent disease and two deaths. In this report they noted that in almost every instance of recurrence a more conservative procedure than radical vulvectomy and inguinal lymphadenectomy had been performed.

I would like to ask Dr. Figge whether there are any data concerning the type of surgery performed in the 34 patients with a lesion of <2 cm and negative nodes. Were any of these 34 patients in the group of 20 patients noted to have a procedure more conservative than radical vulvectomy? If there was such a subgroup, was the recurrence rate greater?

I would like to congratulate Dr. Figge for bringing to our attention a subject of importance. Vulva carcinoma is most often a disease of elderly, medically compromised patients, and therefore their ability to survive the surgical procedure must carefully be considered. However, in the younger medically uncompromised patient we must be careful not to lessen the chance for cure with less than the most curative surgical approach.

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Dr. John Stapleton, Reno, Nevada. I congratulate Dr. Figge on an excellent paper and an excellent modality of presentation. I would like to ask two questions: (1) In your parameters of evaluation did you look at confluency of the lesion? Isolated reports from the literature state that approximately 80% of the recurrences of early invasion after either ipsilateral or bilateral dissection have had confluent lesions. (2) Do you believe in performing superficial groin dissections, or do you always perform superficial and deep groin dissections?

Dr. Enrique de Castro, Portland, Oregon. In our group we have had two patients with cystadenocarcinoma of Bartholin's gland. One patient was under the care of my associate, Dr. Gerald Kinzel, a member of this society, and the other was a patient of mine. In reviewing the literature I find there have been some changes in the method of treatment and in the spread of this tumor. I wonder whether Dr. Figge would comment on how it relates to vulvar cancer and in general terms on how to proceed with treatment in these two cases.

Dr. Alan King, Loma Linda, California. These kinds of data are needed. We have published data on an identical number of patients with basically the same results. I became interested in early invasive vulvar lesions when we noted a lack of recurrences in patients with small, superficial lesions.

Historically one can divide the treatment of vulvar cancer into four eras. The first is before 1900. We reviewed the German, French, and English literature and found publications dating back to 1826. Treatment was basically local excision, and patients were not doing well. After the turn of the century the French initiated the second era, developing what was to become the standard radical vulvectomy and femoral triangle node dissection. That procedure remained basically unchanged until the start of the third era, the middle of the century when surgeons such as Alexander Brunschwig and Stanley Way popularized an extension of the procedure. This did not result in a significant improvement in salvage. We feel that the fourth era began in 1970 when Franklin and Rutledge published the initial paper concerning the early invasive vulvar lesion. Since then about 200 cases have been reported. No surgeon has a large volume of these cases. We had 24 in 15 years, the data being published in *Gynecologic Oncology* this past summer. These were Stage I lesions of <2 cm in diameter and with >5 mm of invasion.

Varying results have been reported. I think it is safe to say that with Stage I lesions of 1 or 2 mm of invasion the incidence of lymphatic involvement is minimal. We do not really know—we need more data. This paper is a significant contribution.

Dr. Robert Futoran, Los Angeles, California. In 1973 we reported a case that had contralateral metastatic lymph nodes with microinvasive carcinoma. I think this was the only one reported since the paper by Dr. Rutledge. It shows that it can occur, but it is extremely uncommon. In fact, some of our proctologists do not perform lymph node dissection with anal cancers. They feel that if the tumor recurs locally it can be operated on at a later date. I do not really support that philosophy. The question I have is with reference to carcinoma in situ. We have become less aggressive and find they recur. Have you seen a recurrence of carcinoma in situ in any of the 153 cases?

Dr. Michael Turko, Vancouver, British Columbia, Canada. I would also like to congratulate Dr. Figge for bringing this to our attention. His study confirms what we have discovered in our center—that the most important prognostic factor in vulvar carcinoma is the presence or absence of lymph node metastasis. Smaller lesions are being diagnosed earlier in the younger patients, and individualization of surgical treatment is being undertaken at the Cancer Control Agency of British Columbia. I would like to ask Dr. Figge three questions: (1) How were the patients with recurrent disease managed—that is, did they have radiotherapy? (2) Did any patients with positive nodes have postoperative radiotherapy? (3) Did any patients that developed recurrence have positive margins?

Dr. Figge (Closing). Patients with recurrent disease were managed in a variety of treatment patterns that we felt were appropriate. Radiation therapy was employed in at least a third of these instances.

If positive nodes are encountered during the operation we will frequently, but not invariably, advise subsequent radiation therapy. The decision rests upon the number of nodes involved and their location and whether extranodal extension is present.

I am not aware that any of our recurrences were characterized by positive margins in the original surgical excision. We have seen carcinoma in situ recur after a radical operation for vulvar carcinoma, and such cases have not been included in the table presented in this review.

In all but two of the 24 instances of recurrent carcinoma the original treatment was considered retrospectively to be adequate and consisted of at least radical vulvectomy and bilateral groin dissection.

We did not evaluate confluency of the lesion as an independent variable, since this would apply only to a small number of the cases and probably did not influence treatment. I would certainly agree as to its potential significance in microinvasive carcinoma, and it should be considered in any prospective study.

I believe that carcinoma of Bartholin's gland is a distinctly separate entity from squamous carcinoma of the vulvar skin. It does not lend itself to conventional staging, its pathways of spread are probably different, and its patterns of recurrence are dissimilar. We feel it should always be approached in an aggressive and radical fashion.

At present we are reluctant to limit our groin node dissection or sampling to the superficial nodes alone but do go beneath the cribriform fascia to remove the femoral nodes.

Dr. Spanos, I am, of course, familiar with the report of the Task Force of the International Society for the Study of Vulvar Disease. The report is based on three observations: (1) The majority of Stage I vulvar cancer falls into their definition of microinvasion. (2) These cases exhibit the same propensity to metastasize to lymph nodes, to recur, and to result in death. (3) Conservative operations frequently lead to an increased risk of recurrence and death. It is this third assumption that may be contested. The 388 cases reviewed were hardly a homogeneous population. Depth of invasion was limited to 5 mm but measured in some instances from the deepest rete peg. The influence of cellular anaplasia or vascular-lymphatic permeation was ignored although exclusion of such cases in at least one of the reports would have removed all cases with node metastases. The contention that a conservative operation more frequently leads to recurrence and death is hard to support from their data. Of the six deaths detailed within the report three occurred despite radical vulvectomy and groin dissection. The incidences of recurrence among patients treated by radical operation and a more conservative approach, 15.60% and 24.39%, respectively, do not differ statistically ($p = 0.288$). Hacker et al. observed an identical incidence of local recurrence in 27 patients similarly defined.

It is becoming increasingly apparent that there is a subset of patients with early carcinoma of the vulva in which an aggressive pattern of behavior will be observed. The frequency and pattern of recurrence in such patients may be to a large degree independent of the degree of radical treatment. Rather than contend that all patients with early disease be invariably treated by a radical procedure, it would seem appropriate to redirect our attention toward identifying and defining the characteristics of aggressive lesions so they can be approached as a subject of early invasive carcinoma.

Sterilization failures and their causes

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To say that a sterilization failure rate is expected does not answer why. Forty-seven cases of repeat sterilization have undergone such surgical and pathologic scrutiny. Resection methods failed most frequently because of spontaneous reanastomosis or fistula formation. Fimbriectomy was particularly vulnerable to reanastomosis because the fimbria ovarica was not removed. Mechanical devices failed when the device was defective, placed improperly, or placed in an improper location. Tissue damage was evident but incomplete when the bipolar electrocoagulation method failures were reviewed, and the endosalpinx remained viable. Unipolar method injuries, in contrast, were complete; they failed by fistula formation. Thus bipolar method failures may occur because of the limited range of electrical power available when using bipolar generators. Some sterilization failures are preventable, but many are not. When medicolegal questions arise, these findings may help answer the question, Why? (AM J OBSTET GYNECOL 1985;152:395-403.)

Key words: Sterilization failures, fimbriectomy, bipolar sterilization, mechanical sterilization, unipolar sterilization

Since 1974 this author has performed 47 laparoscopic sterilization procedures upon patients previously sterilized. A protocol was established early in this experience to assess the probable cause for each failure. In 1977 a financial assistance fund was established to help defray the unexpected costs associated with this repeat operation and to encourage referrals. Patients seeking this service came from the Pacific Northwest; six patients were referred from distances exceeding 1000 miles. It is impossible to calculate a failure rate, since the denominator is unknown. This review explores the causes of these sterilization failures and seeks to find problems which may be unique to specific methods chosen for female sterilization.

Material and methods

Prior to each repeat sterilization procedure, a copy of the original operative note and, if available, the pathology report were obtained. In all cases laparoscopy was performed as a short-stay procedure; the snare method of sterilization was used in most cases. Once tubal insufflation with indigo carmine established tubal patency, the likely anatomic area of failure was widely resected. Photographs, when helpful, were taken for later review.

Each specimen was sectioned throughout its entire length and submitted for microscopic scrutiny. During this histologic review a difference between bipolar and unipolar findings prompted an analysis of freshly damaged tissue after each method. To standardize this evaluation, the same generator was used with the same power output (Cameron-Miller, Model 7910 at 43 watts). Five patients with normal tubes were each sterilized by a bipolar energy and a unipolar energy mode. Three centimeters were coagulated over the proximal third of each tube, the bipolar method (Corson forceps) to one tube and the unipolar (Wolf forceps) to the other. Each tube was heated through a visual blanch, swell, and collapse stage of coagulation. The damaged tubes were then resected by the snare technique.

Each method of sterilization was assigned to groups with technical similarities (see Table I).

Results

Each of the nine failures following fimbriectomy had a common finding—a remnant of fimbria ovarica with spontaneous reanastomosis (Fig. 1). Of the six snare sterilization cases studied, two had complete reanastomosis. When analyzed, these two cases had restoration of tubal continuity without evidence of previous electrical damage. This is considered remarkable, since the initial pathology reports confirmed that each of the resected specimens, usually greater than 1.5 cm in length, was indeed fallopian tube. Two of the snare sterilization failures revealed mesothelial fistulas bridging the resection gap. One snare sterilization failure presented as a cornual ectopic pregnancy; another presented as an ectopic pregnancy located in the fimbrial ampulla. In both ectopic cases, endosalpingosis isthmica nodosum was found in the tubal stump attached to the uterus with demonstrated patency.

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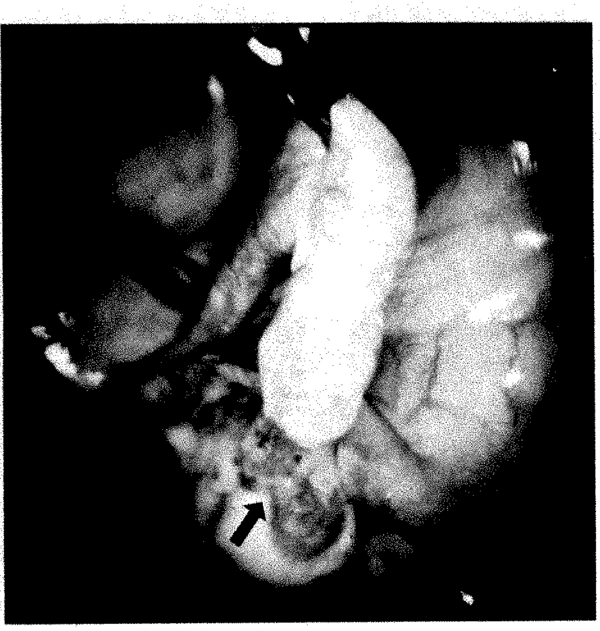

Fig. 1. A typical finding after a fimbriectomy failure—a remnant of fimbria ovarica with spontaneous reanastomosis. *Arrow* overlies the right ovary and points to a remnant of fimbria ovarica.

Following a Pomeroy method, reanastomosis was evident in one case; the rest presented as fistulas. Chromic catgut, rather than plain catgut, was used in these patients; each procedure was performed during the postpartum period.

All bipolar failures showed the same finding—an intact serosa, coagulated muscularis, and a viable, though constricted, endosalpinx (Fig. 2). The duration of coagulation used during the first sterilization was seldom recorded. None of the reports discussed the power of electrical energy applied, and only three reports discussed the brand of bipolar instrument used for the procedure. Most reported a 2 cm or more burn technique; five were burned and transected. However, two operative reports described only a 1 cm burn applied to each tube. Three failures occurred in bipolar methods which described a cornual ablation; five failures occurred after coagulation of the proximal third of the tube, and one failure occurred following destruction of the middle third.

Fistula formation was found in all of the unipolar sterilization failures, and residual endosalpinx was absent.

A notable difference between bipolar and unipolar injury was seen when freshly damaged tissue was examined. A profound coagulation effect, through and through, was the characteristic finding after a unipolar injury (Fig. 3). Bipolar injuries, however, left a histologic shadow of the endosalpinx, suggesting the potential for persistent viability (Fig. 4). This possibility is supported by all of the histologic findings in the bipolar failures. Three patients, who chose to terminate their pregnancies, were resterilized at the same time. The decidual reaction of pregnancy was found in the "coagulated" endosalpinx, confirming persistent viability (Fig. 5.).

Table I. Failures by method

	No. of cases
Resection methods	
Fimbriectomy	9
Snare resection	6
Pomeroy	3
Electrical methods	
Unipolar	3
Bipolar	9
Mechanical methods	
Silicone ring	4
Bleier clip	3
Hulka-Clemens clip	1
Weck clip	6
Silk ligation	1
Operator error	
Round ligament resection	1
Round ligament ring	1
Total	47

Mechanical methods

The six Weck clip sterilization failures revealed patency despite the use of double clips on each tube. Hysterosalpingograms revealed bilateral patency in five patients (Fig. 6.). The sixth patient, with unilateral obstruction, was noted to have complete vascular occlusion to the segment of tube located between the double clips—the clips were placed in a V formation with atrophy grossly evident between them. The other side, as with the other five cases, was patent, and these clips were found parallel to one another.

Each Bleier clip failure appeared to have proper clip placement, but patency through the clip was verified by tubal insufflation. Each patient had requested clip sterilization the first time for personal reasons and requested a Hulka-Clemens clip application for the repeat procedure. Thus a resection analysis was not possible.

The single case of a Hulka-Clemens clip sterilization failure revealed two clips on the patent tube. One clip was located 5 cm from the cornu and was incompletely applied. The second clip was placed distal to the first clip and appeared to engulf the entire diameter of the tube. This clip was therefore located 3 cm from the fimbria. Indigo carmine dye injection, however, confirmed patency despite these two clips.

All silicone ring failures presented with the same gross and histologic findings. First, though the knuckle

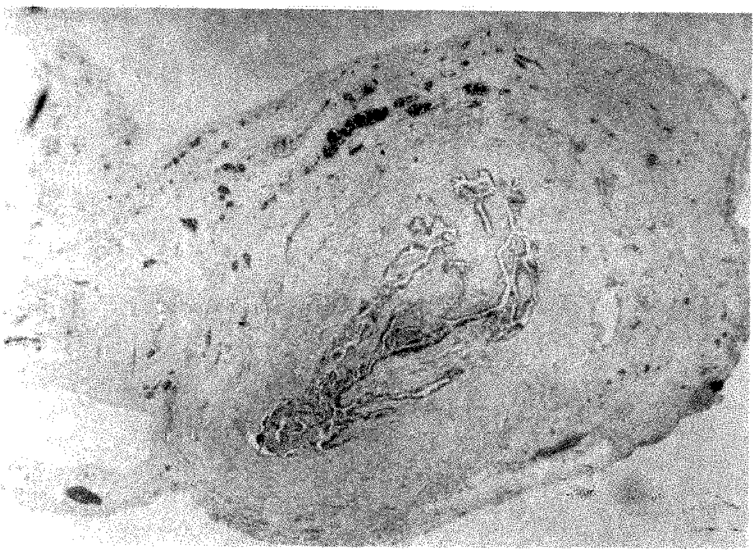

Fig. 2. A bipolar failure with evidence of partial coagulation of the muscularis. Vascularity persists in areas, and a viable endosalpinx is noted.

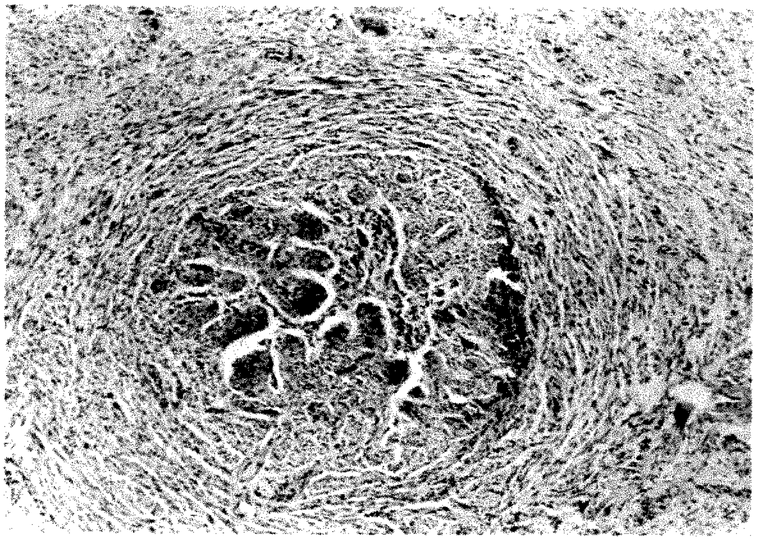

Fig. 3. Complete, through-and-through, coagulation effect of freshly damaged fallopian tube after a unipolar injury.

of tube had atrophied, the viable ends had not separated. Second, fistula formation under the ring was easily identified (Fig. 7.)

One mechanical method deserves special mention. An "incidental tubal ligation," following a cholecystectomy, was performed: Black silk was used as a single tie around the middle third of each tube. These single ligatures were passed through the mesosalpinx and tied. Photographs taken during the repeat sterilization operation revealed bilateral patency; histology confirmed patent ligatures.

Two overt operator errors were discovered. The first was a round ligament application of the silicone ring during a difficult minilap procedure. The primary surgeon, suspicious of this potential problem, counseled the patient and referred her for hysterosalpingogram and subsequent laparoscopy. The second error was an electrocoagulation of the left round ligament. It is of interest that the primary surgeon in this case was an experienced laparoscopist.

Comment

There is no perfect sterilization method—for female or male. When failures occur, the cause should be evaluated. A common cause, repetitive in nature, might signal a surgeon to reassess the old or invent the new. Frequently methods of sterilization are chosen because one method, according to a recent review, has the "best

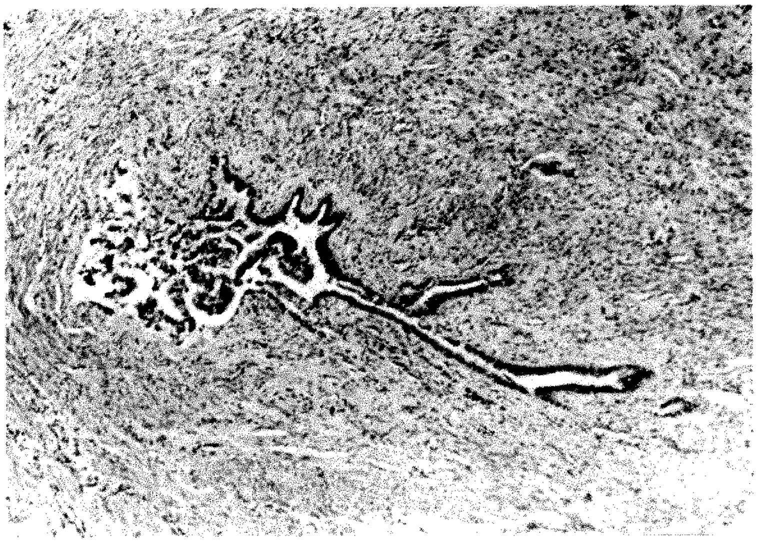

Fig. 4. Freshly damaged fallopian tube following a bipolar injury. A histologic shadow of the endosalpinx suggests the potential for persistent viability.

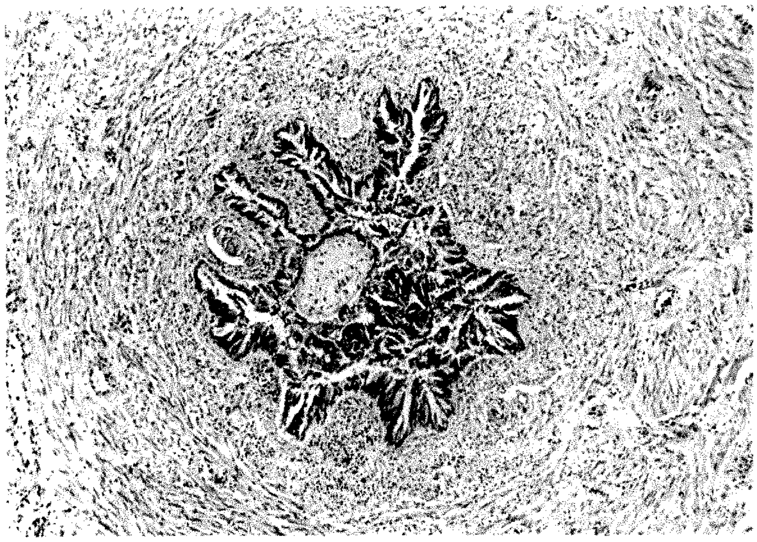

Fig. 5. A bipolar failure studied at the time of a termination of pregnancy. Viability of the endosalpinx is confirmed by the presence of a decidual reaction of the epithelium.

failure rate." Each such report must be analyzed for statistical confidence, duration of follow-up, and loss to follow-up statistics. Cumulative studies are difficult to assess because each author may use different criteria for the failure statistics.[1-4]

Sterilization procedures damage or impede the function of normal tissue. The body's attempt to reestablish continuity is evident by those cases of reanastomosis and fistula formation. Also, an iatrogenic pathologic condition, such as endosalpingosis nodosum, can lead to sterilization failure.[5] Incomplete resection, incomplete mechanical obstruction, and unproved methods further increase the risk of sterilization failure.

A review of the literature regarding fimbriectomy deserves special mention. In May, 1969, Kroener[6] reported the personal experience of his father's method of total fimbriectomy. Special note was made in that report which referred to the fimbria ovarica. Emphasis was placed on a separate surgical step necessary to ligate that structure to reduce the failure rate. Later, several reports denounced the Kroener procedure; each, however, altered the technique and made no mention of a fimbria ovarica ligation.[7-9]

In the mid-1970s the unipolar failure rate was extremely low; however, isolated reports of electrical injuries during unipolar sterilization spurred interest in another electrical method—bipolar.[3, 10-12] The physics of electricity, however, restrict the quantity and force

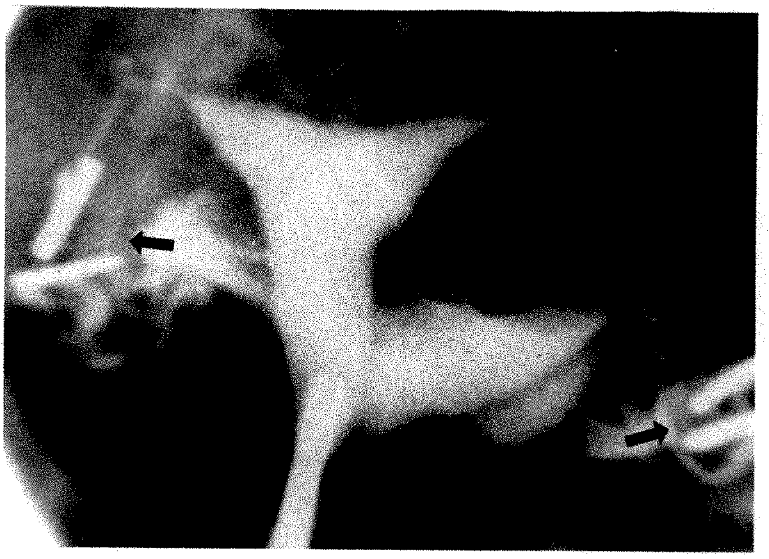

Fig. 6. A hysterosalpingogram reveals bilateral tubal patency following a Weck clip sterilization failure. *Arrows* point to double clip application on each patent tube.

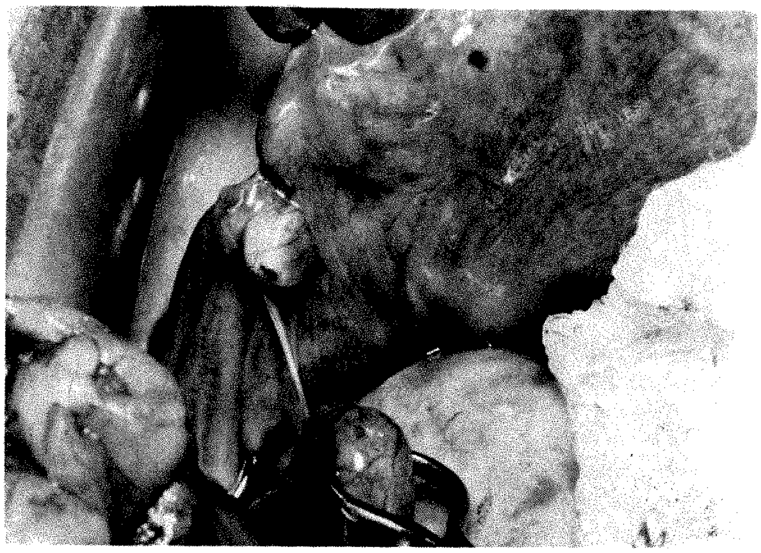

Fig. 7. A silicone ring failure with a fistula formation rather than the intended separation of the viable ends.

of energy when bipolar forceps are used. Design restrictions limit the extent of tubal damage; more areas of application are necessary and for longer periods of time.[13] Ironically, there is little information available in the literature which describes how much tissue to destroy.

Unipolar experience has been extensive, and follow-up has been long.[3, 10, 11] Bipolar experience in the early 80s has also been extensive, but follow-up is relatively short.[4] The histologic characteristics of freshly damaged tissue under standard conditions are disturbing; they suggest inadequate coagulation of the deeper tissue when bipolar methods are chosen. Should vascular coagulation be incomplete, the viability of the endosalpinx is a possibility. Each bipolar failure confirmed this integrity. Logic would dictate that complete vascular obliteration must be assured to arrive at the lowest failure rate; extensive and prolonged bipolar energy is therefore necessary. Transection procedures, in conjunction with bipolar methods, were not absent from this failure series.

Mechanical methods are limited by their specific design. Proper placement in the isthmic portion of the fallopian tube is necessary when mechanical devices are used. Yoon,[14] the inventor of the Falope ring, cautions the surgeon when confronted with a "fat" tube; a slip-page or "milking off" effect can occur if a band is placed on such a tube, or if the band is placed in an area of the ampulla. In all cases, if necrosis of the tubal loop is delayed, apparently a fistula under the band may develop.

As with the band, placement of the Hulka-Clemens clip on the isthmic portion of the tube is critical for proper occlusion. In addition, care should be taken to place the clip completely around the tube and as perpendicular to the axis of the tube as possible.[15]

Bleier clip failures may be in part due to a design defect. In this series, as well as in an unpublished experience of Adelman with 16 Bleier clip failures, patency was a common finding even after proper placement on the isthmic portion of the fallopian tube was confirmed.

Weck clips were not designed for female sterilization. Simply stated, they should not be used.

Failure rates for several well-established sterilization methods have been published over the years. Surgeons should counsel their patients to expect a small, unavoidable failure rate. Newer techniques, however, are being employed without the availability of long-term follow-up. This author is particularly concerned about a potential rise in bipolar sterilization failures. Surgeons should exercise caution when utilizing new techniques and pay careful attention to detail when performing well-established techniques of sterilization. Several conclusions regarding the causes of these sterilization failures appear to be justified: (1) During fimbriectomy, specific attention should be directed to the complete ligation and removal of the fimbria ovarica. (2) Mechanical devices used for the purpose of tubal occlusions should be properly designed, placed properly, and positioned in the proper place on the isthmic portion of the fallopian tube. Also, mechanical devices should be tested, as are drugs, prior to market approval. (3) Electrical coagulation of the fallopian tube must destroy the vascular supply to enough tubal tissue to assure luminal obliteration once the healing process is complete. Unipolar energy appears to meet this requirement much more easily than bipolar methods. The physical difference between these two energy applications requires a careful selection of compatible bipolar instruments and generators.[13] When compared to unipolar coagulation, prolonged coagulation time should be the rule with use of bipolar methods. Though the literature is devoid of clear recommendations, tubal coagulation for a minimum of 2 cm seems a reasonable recommendation to achieve the desired effect—permanent atrophy of a tubal segment. (4) Normal tissue has a remarkable propensity to heal and reestablish continuity. No wonder the perfect tubal sterilization method has eluded the gynecologic surgeon.

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Discussion

DR. KEITH P. RUSSELL, Los Angeles, California. Dr. Soderstrom has presented an interesting and valuable analysis of one of the current concerns in modern obstetrics, especially since the operation of sterilization is now the most common gynecologic surgical procedure, with a frequency exceeding dilatation and curettage. The medicolegal implications are obvious. The author has analyzed for us the various types of sterilization failures associated with the different procedures in use today. Although the general findings associated with sterilization failures are commonly known, he has classified these in such a way that we can better understand the manner in which they do occur.

The author was unable to provide us with any incidence figures, since the referral pattern that brings these cases to him does not lend itself to a valid statistical occurrence analysis. However, we do know that sterilization failures have followed every known method of tubal interruption, even including hysterectomy. There are documented cases in the literature, though quite rare, in which pregnancy has occurred in spite of a previous hysterectomy.

Dr. Soderstrom has shown that failures result from incomplete removal of vital parts of the oviduct, from incomplete interruption of the tubal lumina, from recanalization of a previously destroyed or removed segment of tube, or from outright failure to perform the procedure properly, for instance, ligation of a round ligament, or application of an occlusive ring to a round ligament rather than to a tube.

In reviewing a number of similar cases, usually for legal considerations, it is my experience that commonly the truly negligent procedure can be differentiated from the unavoidable failure by reviewing the interval of time from the procedure to the failure, that is, the occurrence of pregnancy. In those cases where the procedure has been negligently or incompletely performed, pregnancy usually ensues within 3 to 6 months following the procedure. In those cases in which recanalization appears to be the underlying causation of failure, usually a number of years (2 to 5) have passed following the procedure. The latter group of cases can often be satisfactorily defended, the former group with difficulty.

A review of Dr. Soderstrom's informative report prompts a number of questions: Should all patients undergoing voluntary sterilization have follow-up salpingograms or other tubal patency tests after the procedure? If so, how soon? Should patients be advised to use another form of contraception for a period of time following the procedure (3 to 6 months) while awaiting proof of permanent sterilization? What is the author's preferred method of female sterilization, and in particular, when a repeat procedure is being carried out?

From a personal standpoint, my own preference for this procedure is partial resection of each tube, removing not less than a 1.5 cm segment of the midportion. We increase the success rate by adding cauterization of each of the cut ends of the tubes, together with the usual ligation of each tube. When possible, we also attempt to bury the tubal ends in the mesosalpinx and oversew the interrupted area to ensure to the greatest extent possible that spontaneous reanastomosis or recanalization does not occur and to reduce the incidence of adhesions.

Dr. Simon Henderson, San Francisco, California. I would like to make one or two comments about your allusion to fimbriae remaining after fimbriectomy. I think the finding of "fimbriae" can be mistaken for "plicae" with actual outfolding of the ampulla so it resembles the fimbrial end of the tube which has been removed. If you cut through the ampulla about 1 cm proximal from the fimbriae, the plicae look like fimbriae, but they are not. They are inverted plicae.

This reminds me of a case in which I gave a medicolegal opinion regarding a pregnancy which occurred following a fimbriectomy. The resident physician, who had done the bilateral total salpingectomy the second time around, testified that fimbriae appeared to be present. The pathologist also reported fimbriae at the end of this particular tube. However, the tube was only 5 cm in length. Of course we know that tubes should be 10 to 12 cm long. So these reported fimbriae could not possibly be fimbriae. A review of the original pathologic findings at the time of the fimbriectomy showed fimbriae were indeed present and were therefore totally removed. I think this illustrates my initial point.

In view of continuing sterilization failures we need to look to the urologists. Initially, they had a number of failures with vasectomy. They did double crushes, burns, tying the vas backwards and forwards, and even doubling the vas back on itself in an attempt to prevent these failures. Finally, they used intraluminal cautery, which produced an intraluminal scar and had fewer failures. Today it is rare for vasectomy to fail if intraluminal cautery has been performed.

With regard to my own work with sterilization reversals, I have been amazed at the number of patients with proximal tubal fistulas identified by hydrotubation done just prior to performing the anastamosis. In patients who had unipolar tubal cautery performed close to the uterus, I find about one in five with small fistulas. So there must be a lot of women with fistulas who are not getting pregnant.

Dr. Ralph Hale, Honolulu, Hawaii. There is an ongoing prospective study called the CREST Project under the auspices of the Centers for Disease Control of which I happen to be one of the principle investigators. One of the points of information that is coming out is going to be a prospective look to give a denominator. A preliminary item which we have already found in just 2 years is that the rate of failure for sterilization is much higher than any of us had ever really thought. Unfortunately, we are not evaluating the unilateral or bipolar coagulation; we are a part of a study that is evaluating minilaparotomy and postpartum tubal sterilization. I used to tell my patients that the failure rate was about one in a couple of thousand or so, because that was what was reported. We are finding in this preliminary 2-year study a failure rate of about one in 1000 or less—and with the clip and the Falope ring it is even higher. I feel the problem is the technique used by the individual. I would like to make some comments about what we have found regarding bipolar coagulation and what we have confirmed in some lower animal studies. When you perform bipolar coagulation, a major problem is a lack of depth of the bipolar coagulation. One of the techniques used with bipolar coagulation is examination not only of the coagulation but also of the cutting and division of the tube. If you do see fluid return, even if it is not blood, most likely an inadequate amount of coagulation has taken place and that particular patient needs to be recoagulated to complete the desiccation and hopefully to prevent the occurrence of fistula formation. I think this is one of the things we do not teach physicians about coagulation.

Dr. Clifford Curtis, Redwood City, California. I would like to present briefly the case of a woman who underwent laparoscopic sterilization by the unipolar method. The operation was performed in 1973; in 1974 the method failed, and she had a second sterilization with therapeutic abortion. This time there was actual removal of a tubal segment on the right. She subsequently had a third laparoscopy, primarily for the diagnosis of pain. The operative report did mention that the tubal segments were widely separated. I first saw the patient in the emergency room in 1980 with a history of irregular menstrual periods, pain, and hypotension. At the operation we discovered a 2500 ml hemoperitoneum and confirmed the previous laparoscopy and that indeed both tubes were interrupted in midcourse—3 cm on the left and 4 cm on the right. On the posterior surface of the right broad ligament there was a 4 by 3 cm shaggy, bleeding area and a right salpingo-oophorectomy was performed. In the postoperative course the patient's packed cell volume of 14 was raised to 31 by 4 units of blood. The pathology report showed connective tissue from the right broad ligament with chorionic villi. There was syncytiotrophoblast on the right peripheral uterine tube segment, and the right ovary was the site of the corpus luteum. It was presumed there was a fistula formation in the proximal tubal segment that led to the abdominal pregnancy. I would like to ask Dr. Soderstrom if he has any ideas about the handling of this proximal tubal segment as far as the location for coagulation and whether he has any method that would prevent this fistula formation.

Dr. Franklin D. Loffer, Phoenix, Arizona: Dr. Soderstrom's paper, as usual, is a valuable and clinically important one. I would like to limit my comments to his discussion of failures of bipolar tubal coagulation. His data should give us concern if it represents a widespread and growing problem. I do not think, however, there is any published evidence to suggest this will be an increasing problem. Indeed, my own personal series of approximately 3000 cases does not show an increased risk of pregnancy with bipolar tubal coagulation.

In the first half of my own series, in which unipolar was used, there have been identified four pregnancies, one of which was an ectopic. There have been three pregnancies, all ectopics, in the last (bipolar) half. It is true that the number of sterilization failures that occur increase with time, and therefore my unipolar and bipolar group are not strictly comparable. In fact, the earliest any of my patients became pregnant was 27 months after their sterilization, and my bipolar group contains patients operated on as recent as 3 months earlier.

You could also question the apparently good published results of the bipolar group by the fact that authors generally report good results. For some strange reason there is little motivation to publish bad results. In addition, authors who publish tend to have large series and therefore a great deal of experience whereas the occasional operator, who may have poorer statistics, never appears in the literature. Follow-up is also an important feature and as Dr. Soderstrom mentioned, many patients do not return to their operating surgeon. Published series also often ignore follow-up rates, and sterilization is not an example of "no news is good news."

So Dr. Soderstrom's presentation has the advantage of allowing us to see a group of failures and to compare the features they hold in common. Most of the coagulation failures he reported were bipolar, and yet more unipolar sterilization is used in his community. This would indicate bipolar is a poorer procedure. It seems to me, however, that his paper suggests that it is the inappropriate use of bipolar tubal coagulation rather than the procedure itself that is the culprit. One could then ask the question "why not use unipolar?" if adequate sterilization is more readily accomplished. I think Dr. Soderstrom would like to see us use more unipolar sterilization. I stopped using unipolar coagulation, not because I had any electrical problems but for the same reasons I am sure many of you also stopped. The downside risk of unipolar sterilization is bowel injury. Even though not all bowel injuries are necessarily related to electrical current, a large number of them are and the bad results are harder to explain than a pregnancy.

Both unipolar and bipolar methods are good, acceptable techniques. I think they are equally good in their ability to provide sterilization. It is the technique used and not the method that is the issue. Rather than argue about which one is better, our concern should be, Are they being used correctly by our students and practitioners?

I do have one question for you. What length of time after the initial sterilization have the failures occurred? The reason I ask this question is, I would expect to see pregnancies occur much more frequently in the bipolar group if indeed we are leaving intact lumen with good epithelium.

Dr. Soderstrom (Closing). Herbert Peterson from the Centers For Disease Control studied a large sterilization series from Singapore looking at failure rates. A cumulative failure rate of 85% occurred within 2½ years. The longest period of time was 15 years. In my series the longest was 8 years. To answer the second question regarding hysterosalpingogram following surgery, a number of articles have demonstrated the hysterosalpingogram has no value in evaluating tubal patency and may indeed create tubal patency. I have seen patency occur during hysterosalpingogram for evaluation prior to tubal reanastomosis. Because of my teaching responsibilities, I try to teach the house officers all of the methods. Personally, I prefer the tried and true 2 to 3 cm of electrocoagulation with use of the unipolar method rather than the bipolar method. The method that I recommend for repeat sterilization is tubal resection and microscopic analysis. One should serially slice the entire tube, for it may appear normal. We owe such an examination to the patient as well as the primary surgeon for medicolegal reasons. The comment regarding plica vervus fimbria ovarica makes a good point. I made the diagnosis of fimbria ovarica because in every case this tissue was grossly adherent to the ovaries, which by definition is fimbria ovarica. I do not know how to recoagulate the tube to prevent recurrent tubal sterilization failures. Endosalpingosis was previously described by Dr. McCausland before this Society, but I am not able to tell whether it would be preferable to burn the uterine cornu or stay 1 cm away from the cornu. Failure rates were alluded to in my oral presentation, and I would like to leave you with this problem. Dr. Richard Kleppinger is the only individual I know who has a large personal series of bipolar sterilization failures. In June of 1984 he presented a series of approximately 4000 cases in which he had 16 failures; however, patient No. 4000 was sterilized in March, 1984. He agreed that the cumulative failure rate over 2½ years is unknown. The bipolar failures in my series occurred in less than 1 year. Unipolar failures occurred after 2 years. The clip failures were almost immediately apparent. Fimbriectomy failures occurred within a year and a half.

Evaluation of the use of continuous lumbar epidural anesthesia for hypertensive pregnant women in labor

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The use of continuous lumbar epidural anesthesia in women with pregnancy-induced hypertension remains controversial. We retrospectively reviewed the charts of 285 women with pregnancy-induced hypertension who were delivered in a 2-year period. Among 185 vaginally delivered patients who received continuous lumbar epidural or local anesthesia, there were no significant differences in the incidence of maternal hypotension, abnormal fetal heart rate tracings, low Apgar scores, or neonatal intensive care unit admissions. Of 100 patients delivered by cesarean section, the incidence of low Apgar scores, depressed umbilical cord pH values, and neonatal intensive care unit admission was increased among those who received general anesthesia ($p < 0.05$). However, general anesthesia patients were more likely to have abnormal fetal heart rate tracings (27% versus 4%) requiring urgent delivery. Thus differences in outcome probably reflect poorer fetal condition prior to anesthesia induction rather than a specific anesthetic effect. These results demonstrate that continuous lumbar epidural anesthesia is safe and effective for both the fetus and the mother with pregnancy-induced hypertension. (AM J OBSTET GYNECOL 1985;152:404-12.)

Key words: Epidural, preeclampsia, labor, fetal heart rate monitoring

Although the safety of general anesthesia for delivery of patients with pregnancy-induced hypertension has been established,[1] the use of epidural anesthesia for pain relief in such patients has remained controversial. Some authorities have advocated the use of epidural anesthesia for labor analgesia and control of hypertension in pregnancy-induced hypertension,[2-4] but this view has been opposed by others, who cite the risks of hypotension and consequent fetal distress in such patients.[5, 6]

At the present time no large series documents the safety of epidural anesthesia for patients with pregnancy-induced hypertension. In order to explore this issue, we conducted a retrospective analysis to determine whether fetal and maternal morbidity are altered in patients with pregnancy-induced hypertension who receive epidural anesthesia and to compare the fetal and maternal outcomes among patients delivered with either epidural, general, or local anesthesia.

Patients and methods

Records of 5505 patients who were delivered from January 1, 1981, to December 31, 1982, were reviewed. Patients received care in the prenatal clinics of University of California (San Diego) from resident physicians and nurse midwives under faculty supervision. Maternal and infant data from patients with pregnancy-induced hypertension were coded for further analysis.

The diagnosis of pregnancy-induced hypertension required blood pressure recordings of >140/90 mm Hg on two occasions at least 6 hours apart and one or more of the following: proteinuria >2+, significant nondependent edema, or weight gain of at least 4 pounds in a week. Severe pregnancy-induced hypertension was diagnosed when one or more of the following were present: blood pressure >160/110 mm Hg for >4 hours, visual or cognitive disturbances, proteinuria >5 gm/24 hours, oliguria, pulmonary edema, persistent epigastric pain, and/or elevation of liver transaminases. Patients with chronic hypertension were excluded.

During the period of study 5506 patients were delivered; 285 (5.2% of the total) met the criteria for the diagnosis of pregnancy-induced hypertension. Of these patients 185 (64%) were delivered vaginally and 100 (36%) required cesarean section. Severe pregnancy-induced hypertension was present in 23.5% of the study population.

With the exception of local anesthesia, anesthesia/analgesia for labor and delivery was administered by

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Table I. Maternal outcome with vaginal delivery

	Deliveries with epidural anesthesia (%)*	*Deliveries with local anesthesia* (%)*	*p value*
No. of deliveries	116	69	
Age (yr)	24.9 ± 5.4	24.5 ± 6.2	NS
Pregnancy duration (wk)	39.1 ± 2.3	39.5 ± 1.8	NS
Nulliparity	102 (88)	42 (61)	<0.001
Severe pregnancy-induced hypertension	23 (20)	7 (10)	NS
Use of oxytocin	53 (46)	17 (25)	<0.01
Labor duration			
Stage 1 (hr)	13.7 ± 7.9	9.1 ± 5.0	<0.001
Stage 2 (hr)	1.6 ± 1.2	.8 ± .7	<0.001
Maximum blood pressure (mm Hg)	155/97 ± 18/13	156/100 ± 13/9	NS
Minimum blood pressure (mm Hg)	124/79 ± 18/12	124/78 ± 15/12	NS
Hypotension during labor†	8 (7)	4 (6)	NS

NS, Not significant.

*Mean ± SD.

†Defined as systolic pressure ≤100 mm Hg or diastolic ≤50 mm.

obstetric anesthesiologists. Local anesthesia included subcutaneous perineal infiltration (5 to 10 ml of 1% lidocaine) and/or administration of pudendal blocks (10 to 20 ml of 1% lidocaine), which were performed by the obstetric staff.

Fetal and maternal monitoring. All patients with pregnancy-induced hypertension received hematologic and plasma chemistry screening to document abnormalities of coagulation or renal or hepatic function. Central venous or pulmonary artery pressure monitoring was performed in 37 of the 68 patients with severe pregnancy-induced hypertension. Maternal vital signs were recorded every 5 minutes during initiation or reinjection of anesthesia and at least hourly thereafter. Transient hypotension was managed by positioning the patient on her left side, increasing the intravenous infusion rate, and providing oxygen by mask. Continuous electronic fetal heart rate monitoring was maintained in all patients. When fetal heart rate tracings suggested fetal distress, fetal scalp pH analysis was performed. Twenty-nine fetuses (10%) underwent this procedure. Umbilical cord blood gases were obtained after delivery in 88 (29%) of deliveries.

Technique of epidural anesthesia. The patient's intravascular volume status was assessed by vital signs, urinary output, and when indicated, central venous pressure or pulmonary artery catheter monitoring. Most patients received an initial infusion of 500 to 750 ml of lactated Ringer's solution. Patients with more severe plasma volume contraction received up to 1000 ml intravenously.

The patient was placed in the left lateral decubitus position and a 17-gauge Tuohy needle was inserted into the second or third lumbar interspace. The needle was advanced into the epidural space by the loss-of-resistance technique. A 20-gauge Teflon or nylon catheter was then threaded 2 to 5 cm cephalad, while ensuring the absence of blood, cerebrospinal fluid, or paresthesias. A test dose of 2 ml of 0.25% to 0.75% bupivicaine was injected, and the patient was observed for evidence of hemodynamic instability and unsatisfactory catheter placement. Following assessment of the test dose, 4 to 12 ml of bupivicaine was injected progressively with careful hemodynamic and fetal monitoring. Left uterine displacement was maintained in all patients with a wedge. The level of anesthesia for labor analgesia was approximately T-8 and for cesarean delivery T-2.

Technique of general anesthesia. Rapid sequence induction was accomplished with thiopental sodium and succinylcholine chloride followed by nitrous oxide/oxygen and low concentrations of halothane. During intubation patients whose blood pressures exceeded 160/110 mm Hg received an intermittent infusion of sodium nitroprusside to minimize blood pressure excursion. After delivery a balanced nitrous oxygen–narcotic technique was used.

Management during labor and delivery and after delivery. Patients with severe pregnancy-induced hypertension were delivered within 24 hours of diagnosis. Expectant management was undertaken in patients less than 35 to 36 weeks' gestation with mild pregnancy-induced hypertension unless deterioration of fetal or maternal status occurred. Patients received a 4 gm intravenous loading dose of magnesium sulfate followed by continuous infusion (1 to 2 gm/hr) from the onset of labor/delivery procedures until 24 to 36 hours postpartum. Blood pressure persistently measuring above 160/110 mm Hg was treated with hydralazine, 5 to 10 mg intravenously, to maintain the diastolic pressure between 90 and 100 mm Hg. Pediatricians attended the

Table II. Neonatal outcome with vaginal delivery

	*Deliveries with epidural anesthesia**	*Deliveries with local anesthesia**	*p value*
No. of deliveries	116	69	
Fetal parameters			
Abnormal fetal heart rate	23 (20)	14 (20)	NS
Meconium	24 (21)	7 (10)	NS
Prematurity (<37 wk)	18 (16)	7 (10)	NS
Neonate parameters			
Birth weight (gm)	3217 ± 628	3231 ± 525	NS
Requirement for intensive care unit admission	24 (21)	8 (12)	NS
Apgar score at 5 min	8.6 ± 0.6	8.7 ± 0.6	NS
Apgar score at 5 min <7	1 (1)	1 (2)	NS
Cord pH value	7.28 ± 0.06	7.28 ± 0.12	NS
Cord pH <7.20	1 (1)	2 (3)	NS

*Mean ± SD.

delivery of all preterm or distressed fetuses as well as all cesarean sections.

Maternal outcome was assessed by a review of hospital records. Fetal outcome was assessed for the period of the initial hospitalization, and fetal heart rate tracings were reviewed in detail. To minimize the effect of delivery method on maternal and fetal outcome parameters, cesarean section and vaginally delivered patients were analyzed separately. Four groups of patients were identified for comparison: (1) patients and infants delivered vaginally with epidural anesthesia, (2) patients and infants delivered vaginally with pudendal, local or no anesthesia, (3) patients and infants delivered by cesarean section with epidural anesthesia, and (4) patients and infants delivered by cesarean section with general anesthesia.

Statistical analysis. Continuous data were compared by means of the two-tailed Student's *t* test. Categorical data were analyzed with the χ^2 statistic with use of Yates' correction for continuity. Probability values of ≤ 0.05 were considered significant.

Results

Vaginal delivery: maternal outcome. Maternal predelivery demographic and obstetric factors are detailed in Table I. Vaginally delivered patients received either epidural or local anesthesia. When the epidural and local anesthesia groups were compared, patients were similar in age, incidence of severe pregnancy-induced hypertension, and pregnancy duration. However, a trend toward lower parity and increased use of oxytocin was observed in the epidural anesthesia group (88% of epidural patients were nulliparous versus 61% of local anesthesia patients; $p < 0.001$).

Blood pressure variations in the epidural and local anesthesia groups were largely indistinguishable. The mean maximum blood pressures recorded in labor were similar (155/97 versus 156/100 mm Hg; probability, NS) as were the lowest blood pressures (154/79 versus 124/78 mm Hg) and incidence of hypotension (blood pressure <100/50) (7% versus 6%, respectively).

One significant difference noted in the outcome of vaginally delivered patients was the longer duration of labor in the epidural group (15.3 versus 9.9 total hours in labor; $p < 0.001$). The association of epidural anesthesia and slower progress in labor was further analyzed to allow for differences in parity and use of oxytocin between the epidural and local anesthesia groups. Considering only nulliparous patients with spontaneous unaugmented labor, epidural patients averaged 12.7 hours in stage 1 whereas local anesthesia patients spent a mean of 8.8 hours ($p < 0.002$). Stage 2 was proportionately prolonged as well (1.7 versus 1.1 hours; $p < 0.01$). This association was also statistically significant for parous patients ($p = 0.02$).

Vaginal delivery: fetal outcome. Fetal and newborn outcome parameters are presented in Table II. No significant differences in the incidence of abnormal fetal heart rate, meconium staining, or prematurity were demonstrable between epidural and local anesthesia patients. Fetal heart rate abnormalities were infrequent with both methods of anesthesia (3% to 5%).

No difference in infants delivered with epidural and local anesthesia was evident when the frequencies of low 5-minute Apgar scores (<7) and/or low umbilical cord blood pH (<7.20) were considered. One of 116 fetuses delivered with epidural anesthesia was asphyxiated. In this case the cord pH was 7.18, the fetal heart rate tracing revealed no significant abnormalities, and the infant recovered normally in the nursery. Of seven neonates whose mothers received epidural anesthesia and whose fetal heart rate tracings were suspicious, all had 5-minute Apgar scores and umbilical cord pH in the normal range. Of the infants delivered with local anesthesia, two of 69 were acidotic at birth (pH of 7.05 and 7.18). Overall fetal morbidity defined

Table III. Cesarean delivery indications

	Deliveries with epidural anesthesia (%)	*Deliveries with general anesthesia (%)*
No. of deliveries	85	15
Failure to progress	41 (48)	2 (13)*
Fetal distress†	4 (5)	9 (60)*
Breech/transverse	13 (15)	2 (13)
Failed induction	11 (13)	1 (7)
Repeat cesarean delivery	5 (6)	1 (7)
Unripe cervix	8 (9)	—
Other	3 (4)	—

*$p < 0.001$.
†Diagnosed by ominous fetal heart rate tracing and/or scalp blood pH ≤7.20.

Table IV. Maternal outcome with cesarean delivery

	Deliveries with epidural anesthesia (%)*	*Deliveries with general anesthesia* (%)*	*p value*
No. of deliveries	85	15	
Age (yr)	24.9 ± 5.4	28.3 ± 7.5	NS
Pregnancy duration (wk)	37.8 ± 4.1	37.5 ± 4.0	NS
Nulliparity	70 (82)	9 (60)	<0.01
Severe pregnancy-induced hypertension	29 (34)	8 (53)	NS
Use of oxytocin	51 (60)	7 (44)	NS
Duration of stage 1 labor (hr)	17.8 ± 7.2	11.2 ± 7.4	<0.01
Maximum blood pressure (mm Hg)	161/95 ± 17/12	181/111 ± 24/13	<0.001
Minimum blood pressure (mm Hg)	124/72 ± 20/16	125/76 ± 21/19	NS
Hypotension in labor†	11 (12)	4 (27)	NS

*Mean ± SD.
†Defined as ≤100 mm Hg systolic or ≤50 mm diastolic pressure.

by 5-minute Apgar score and umbilical cord pH value was minimal in both groups (approximately 1%).

Cesarean section delivery: maternal outcome. The cesarean section rate in the study population was 36%. These patients received epidural or general anesthesia. Indication for cesarean section differed between the epidural and general anesthesia groups (Table III). Failure to progress in labor was diagnosed more frequently in epidural patients whereas patients who were delivered with general anesthesia had a higher rate of fetal distress (60% versus 5%; $p < 0.01$). Abnormal presentation, failed induction, and prior cesarean section were equally distributed between the two anesthetic methods.

Characteristics of the cesarean delivery group are detailed in Table IV. Epidural and general anesthesia patients were comparable in age, pregnancy duration, incidence of severe pregnancy-induced hypertension, and use of oxytocin. However, when most of the parameters assessed are considered, patients with severe pregnancy-induced hypertension had a higher likelihood of fetal distress and general anesthesia for delivery.

Blood pressure dynamics in labor were dissimilar also. Patients receiving general anesthesia experienced higher systolic pressure and wider blood pressure variation than did the patients with epidural anesthesia during labor and delivery. Hypotension was more frequent during general anesthesia (27% versus 12% of patients), although the difference was not statistically significant. No maternal deaths or long-term maternal morbidity occurred in either group. As was noted in the vaginally delivered group, use of epidural anesthesia was associated with significantly longer labor (17.8 versus 11.2 hours; $p < 0.01$).

Cesarean delivery: fetal outcome. As shown in Table V, the frequency of meconium staining and prematurity was not significantly different between the epidural and general anesthesia groups. However, abnormal fetal heart rate and acidosis at birth were observed more frequently in infants delivered with general anesthesia. Eight of nine fetuses delivered with general anesthesia because of fetal heart rate abnormalities were acidotic at birth (cord pH <7.20). Of four infants delivered for fetal heart rate abnormalities with epidural anesthesia, two were acidotic (cord pH of 7.15 and 7.09). The

Table V. Neonatal outcome with cesarean delivery

	Deliveries with epidural anesthesia (%)*	*Deliveries with general anesthesia* (%)*	*p value*
No. of deliveries	85	15	
Fetal parameters			
Abnormal fetal heart rate	20 (24)	9 (60)	<0.01
Meconium staining	13 (15)	2 (13)	NS
Prematurity (<37 wk)	22 (25)	5 (33)	NS
Neonate parameters			
Birth weight (gm)	3072 ± 1090	3412 ± 932	NS
Requirement for intensive care unit admission	25 (29)	9 (60)	<0.05
Apgar score at 5 min	8.42 ± 1.06	6.2 ± 2.68	<0.001
Apgar score at 5 min <7	6 (7)	8 (53)	<0.001
Cord pH value	7.28 ± 0.07	7.16 ± 0.18	<0.001
Cord pH <7.20	3 (4)	8 (53)	<0.001

Table VI. Neonatal complications

	Deliveries with epidural anesthesia (%)	*Deliveries with general anesthesia (%)*	*Deliveries with local anesthesia (%)*
No. of deliveries	210	15	69
Intensive care admissions	49 (23)	9 (60)*	8 (12)
Diagnosis			
Poor transition	13	2	6
Respiratory distress syndrome/premature	13	2	
Sepsis or ruling out of sepsis	10		
Asphyxia	6	1	1
Death	3	2	
Erb's palsy	1		
Torch syndrome	1		
Growth deficiency	2	2	1

*p < 0.001 compared to epidural anesthesia.

differences in neonatal Apgar and acid-base status at birth between epidural and general anesthesia patients were highly significant ($p < 0.001$) but probably reflect the generally poorer maternal and fetal condition prior to induction of anesthesia in the general anesthesia group rather than any specific anesthetic effect.

Neonatal complications. Neonatal complications requiring admission to the newborn intensive care unit for each type of anesthesia are presented in Table VI. Infants delivered with use of local and epidural anesthesia experienced complication rates that were qualitatively and quantitatively similar. Prematurity and transitory respiratory difficulties accounted for most intensive care unit admissions. Slightly over half of the infants delivered with use of general anesthesia were admitted for intensive care unit care, a significantly ($p < 0.001$) increased rate when compared to the epidural and local anesthesia patients.

Five perinatal deaths occurred in the series (perinatal mortality, 16.8/1000). Three deaths were in the epidural anesthesia population: two of prematurity (weight 1045 and 760 gm, 5-minute Apgar scores of 8 and 9) and one death of a second twin which occurred before admission. Two deaths occurred in the general anesthesia group: one neonatal death of an infant with trisomy 18 and one intrauterine death with group B streptococcal sepsis. The distribution of perinatal deaths among the three methods of anesthesia was not significantly different from random results, and no deaths were related to method of delivery or anesthesia.

Anesthesia complications. Few complications attributable to the effects of anesthesia were noted. No complications were recorded with the use of local anesthesia. Two cases of prolonged apnea after general anesthesia were attributed to atypical cholinesterase reactions. An episode of apparent cardiac asystole occurred during a period of hypotension following cesarean delivery with epidural anesthesia. Intravenous ephedrine rapidly restored cardiac activity and blood pressure. Five epidural patients complained of postural headache after delivery. Dural puncture was indicated as the cause of cephalgia in three patients.

Marked hypertensive responses were observed in two thirds of patients with pregnancy-induced hypertension during intubation for general anesthesia. Five patients required sodium nitroprusside to control hypertension, with a mean maximum pressure recorded during intubation of 198/118 mm Hg (range 170/100 to 240/120). Patients not given sodium nitroprusside during intubation experienced a mean peak pressure of 181/118 mm Hg (range 180/110 to 190/130). Additionally, four general anesthesia patients became markedly hypotensive and required pressor agents to restore blood pressure. No cardiovascular or neurologic sequelae of hypertension were noted following delivery.

Comment

This retrospective study surveyed maternal and fetal outcomes following delivery with epidural, general, and local anesthesia in patients with pregnancy-induced hypertension. The analysis compared the outcomes of patients delivered vaginally and by cesarean section separately to minimize the contribution of delivery mode.

Vaginally delivered patients were well matched for maternal and fetal risk factors. Both mothers and neonates had equally excellent postdelivery outcomes as well. Hypotension and fetal heart rate abnormalities as well as the frequency of neonatal intensive care unit admissions were rare. Thus no increase in maternal or fetal risk could be demonstrated when epidural anesthesia was elected.

Patients delivered by cesarean section differed markedly in predelivery risk factors and outcome. Over half the general anesthesia patients had manifestations of severe pregnancy-induced hypertension, compared to a third of the epidural group. Abnormal fetal heart rate patterns were recorded in 60% of the general anesthesia patients, but less than 25% of the epidural patients exhibited such patterns. Similarly, neonatal morbidity (depressed Apgar scores, umbilical cord acidemia, and requirement for neonatal intensive care unit admission) occurred in over half of the patients delivered with general anesthesia, but in less than one fourth of the epidural patients. Thus differences in outcomes associated with the two anesthesia methods in all likelihood reflect the poorer maternal and fetal condition before delivery in those for whom general anesthesia was selected rather than the anesthesia technique itself. The experience with patients delivered by cesarean section underscores the frequent difficulties with control of maternal blood pressure and maintenance of fetal homeostasis when pregnancy-induced hypertension complicates cesarean delivery, regardless of the method of anesthesia used.

Hypotension during anesthesia administration is a major cause of maternal and fetal morbidity.[7, 8] Hollmen et al.[9] reported hypotension during epidural anesthesia in 17% of their normotensive patients. Schifrin[10] reviewed the records of 200 normotensive patients receiving epidural anesthesia and found the incidence of hypotension to be 13%. More significantly, after the hypotensive episode, two thirds of patients developed persistent late fetal heart rate decelerations. Late fetal heart rate decelerations coincident with hypotension during epidural anesthesia administration were also reported by Clark et al.[11] and Matadial and Cibils[12] and McDonald et al.[13]

Hypotension has been reported in 10% to 30% of normotensive patients during epidural anesthesia,[7-9] but patients with pregnancy-induced hypertension appear to be especially susceptible to hypotension and subsequent fetal distress. Although the degree of plasma volume contraction with pregnancy-induced hypertension is variable, most authorities agree that pregnancy-induced hypertension patients demonstrate decreased circulating volume and hypersensitivity to sympathetic blockade. This predisposes the patient with pregnancy-induced hypertension to hypotension during administration of regional anesthesia. Anesthetic blockade of pain fibers in the lumbosacral segments also blocks the sympathetic fibers that modulate vascular tone in the resistance arterioles of the pelvis and lower extremities. If sympathetic blockade reduces vascular resistance more rapidly than volume redistribution and cardiac compensation occur, hypotension may ensue. Maternal hypotension reduces uterine blood flow and oxygen delivery to the fetus, which may then precipitate fetal distress. These effects are magnified when circulating volume is further compromised by uterine compression of the inferior vena cava when the patient is supine. The incidence of hypotension during regional anesthesia can be reduced by displacing the uterus to the left, injecting the anesthetic in a slow incremental manner, and ensuring that adequate circulating volume is maintained. However, because of the inherent risks described, several prominent authorities have advised the exclusive use of general anesthesia for operative delivery of patients with pregnancy-induced hypertension.[5, 6]

The present study differs from previous findings in the lower frequency of hypotension and fetal heart rate abnormalities. In this study the incidence of hypotension at any time during the course of labor with epidural anesthesia was not different than was observed when no anesthesia was given (6% and 7%, respectively). No fetal morbidity related to epidural anesthesia was recorded.

The lower incidence of hypotension in this study may be attributed to several factors. First, maternal intravascular volume status was carefully assessed and corrected prior to initiation of anesthesia. In 12% of patients, central venous or pulmonary artery pressure monitoring was employed to assist in fluid management. Second, the effects of supine posture in aggravating hypotension were minimized by maintaining the patient in a left lateral decubitus position. Third, a small (1 to 2 ml) test dose of anesthetic was administered initially to ensure proper catheter placement and reduce the effects of unintentional intravenous or subarachnoid injection. Fourth, continuing intravascular volume adjustments were carried out with careful fetal and maternal monitoring during instillation of the anesthetic. Fifth, the block was achieved by gradual, incremental administration in order to avoid the rapid onset of sympathetic blockade. Finally, all procedures were supervised by obstetric anesthesiologists with extensive experience in the management of patients with pregnancy-induced hypertension.

It should also be noted that significant difficulties were encountered in the control of blood pressure during general anesthesia. Despite prophylactic nitroprusside infusion during intubation, systolic blood pressures exceeding 180 mm Hg were recorded in over half of the patients. One fourth of these patients became hypotensive as well. The extent to which the wider swings in maternal blood pressure and associated variations in uterine blood flow contributed to the poorer fetal outcome with general anesthesia in this study is difficult to assess. Hodgkinson et al.[14] reported similar marked hypertensive excursions in patients with pregnancy-induced hypertension undergoing general anesthesia and suggested the use of epidural anesthesia to obtain smoother blood pressure control during cesarean section. Marx[3] and Wheeler and Harris[2] have advocated epidural anesthesia for patients with pregnancy-induced hypertension for similar reasons.

An interesting additional finding of this study was the longer duration of labor in patients who received epidural anesthesia. Previous investigations had failed to demonstrate this effect. Brotanek et al.[15] assessed uterine activity after epidural anesthesia and found no change. In a retrospective comparison of labor patterns in patients with and without epidural anesthesia, Crawford[16] detected no increase in the duration of first stage labor although the second stage was consistently prolonged. Matadial and Cibils[12] analyzed uterine activity before and after epidural anesthesia in normotensive gravidas and found no change unless epinephrine was added to the anesthetic. Craft et al.[17] and Gunther et al.[18] also found the first stage duration longer only when epinephrine was used in conjunction with the epidural anesthesia.

In the present study the duration of first stage labor was increased by 50% with epidural as compared to general or local anesthesia. The second stage duration was nearly doubled in the patients receiving epidural anesthesia. This effect was observed even when the analysis was controlled for differences in parity and labor augmentation with oxytocin. However, the etiology of apparent labor prolongation with epidural anesthesia is unclear. Epinephrine was not used in the epidural blocks of this study. It is possible that patients whose labor was proceeding rapidly were not offered epidural anesthesia or that these patients more frequently refused analgesia, which would skew the epidural population toward those of longer labor duration. However, it is possible that lumbosacral neuromotor blockade with epidural anesthesia may reduce the effectiveness of uterine contractions and prolong the time to complete cervical dilatation.

The results of this study demonstrate that overall fetal and maternal morbidity is not increased when epidural anesthesia is administered to patients with pregnancy-induced hypertension. Indeed, epidural anesthesia is generally safe and efficacious for relief of pain during labor and cesarean delivery. However, when considering epidural anesthesia for a patient with pregnancy-induced hypertension, care must be taken to assess and correct intravascular volume accurately and to monitor maternal and fetal vital signs meticulously. Similarly, the possible influence of epidural anesthesia on prolonging labor and precipitating hypotension should be weighed against the benefits of improved blood pressure control and reduced patient anxiety and discomfort. Finally, either epidural or general anesthesia should be administered by skilled individuals cognizant of the pathophysiology of pregnancy-induced hypertension.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. DUNCAN R. NEILSON, Portland, Oregon. The excellent clinical study presented by Dr. Resnick certainly raises some interesting questions regarding the classic teachings in this area of obstetric anesthesia.

The fundamental issue is the role played by sympathetic blockade in the control of uterine blood flow. The most commonly held belief is that epidural anesthesia blocks the lumbar sympathetic outflow causing an increase in vascular capacitance, a decrease in right atrial return, decreased cardiac output, decreased blood pressure, and decreased uterine perfusion. This mechanism of blood pressure control should have disastrous consequences for the fetus. How then can we account for the excellent clinical results reported by Dr. Resnick?

This question is discussed extensively in several publications and in an excellent textbook by Dr. P. Bromage.[1] He points out that the concept of a complete block of the lumbar sympathetic outflow cannot be substantiated in either human or animal models. Much more likely is the situation in which a partial sympathetic block develops slowly and other regulatory processes involving higher reflex centers in the central nervous system compensate, allowing maintenance of normal blood volume and cardiac output. These higher order reflexes can be abolished by the addition of light general anesthesia, and thus their significance can be demonstrated.

Perhaps the most fascinating aspect of this research relates to the mechanism of epidural anesthesia. Rather than passing along the dura, penetrating the extradural nerve roots, and producing a block based primarily on fiber size, it appears that the local anesthetic penetrates the dura and enters the cerebral spinal fluid as if there were no diffusion barrier at all and is taken up by the intradural nerve roots and the spinal cord itself. Selective distribution within the spinal cord then accounts for some of the differential block patterns seen clinically, with relative sparing of certain functions and complete abolition of others. These differential effects are determined by both the type and concentration of the local anesthetic agent. The clinical message here is that results obtained by one technique cannot be generalized to other local anesthetic agents or even to different concentrations of the same agent because of these differences in spinal cord uptake. My suspicion is that some of the dispute in the literature regarding the safety of epidural anesthesia for patients with pregnancy-induced hypertension relates to technical differences of this kind. The authors of the present study chose dilute bupivicaine, which produces one of the most selective patterns of neural block of any agent in current use. Thus I feel the authors have established the safety of the specific method of epidural anesthesia described, but that anyone wishing to vary the technique would be on unproven ground.

I disagree with one point raised by the authors, specifically, the question of length of labor relative to type of anesthesia. The observation reported is that patients receiving epidural anesthesia had longer labors. Later reference is made to the "apparent labor prolongation with epidural anesthesia." I would argue that such etiologic inferences are inappropriate in a retrospective study in which the technique (epidural anesthesia) is not applied randomly to the population. The very fact that epidural anesthesia takes time to administer excludes the most rapidly laboring patients from this modality and thus statistically shifts the mean toward the longer labors. It has also been my experience that the patient with the large fetus firmly wedged in the occiput posterior position is likely to have a long painful labor and a longer than average second stage and is more likely to have a conversion experience in the labor room from her natural childbirth aspirations to a request for epidural anesthesia assistance.

This raises the issue of pain and its effect on the phenomena of pregnancy-induced hypertension. Clinical experience suggests that the pain and other anxiety-producing sensations associated with parturition contribute to the hypertension seen in pregnancy-induced hypertension. Thus practices such as the darkened room and limited visitation are traditionally recommended for the toxemic patient. It is also clear that as the hypertension worsens, especially with the complication of seizures, the outlook for the fetus becomes worse. Therefore it would appear that a major role for epidural anesthesia is the reduction of noxious stimuli and that part of the success of this modality lies in its ability to prevent the otherwise common rise in blood pressure that occurs with advancing labor. The pertinent phenomenon, in other words, may not be the blockade of the sympathetic efferents but rather the limitation of the C fiber afferents. The epidural anesthesia may in this sense become the modern-day equivalent of the darkened room.

The clinical data in this paper fit well with these interpretations. The patients with the most severe and rapidly deteriorating clinical courses had the most compromised fetuses, and those who, despite prolonged labors, received epidural anesthesia that limited the pain input had favorable outcome. The authors also attribute the poorer fetal outcome in the general anesthesia group to the nonrandom allocation of this modality. This certainly seems reasonable, but we are not given any case details; I cannot help but wonder whether some of these patients might not have worsened in the face of excessive noxious input leading to a crisis situation and thus to general anesthesia, and whether such a progression might have been preventable in some cases by epidural anesthesia. I wonder whether a prospective study with random allocation of this modality would not actually demonstrate a superiority of this method rather than merely a lack of contraindication.

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Dr. Thomas Moyers, San Diego, California. Dr. Neilson has confirmed my personal prejudice regarding the use of epidural anesthesia in this situation. I would like to ask Dr. Resnik to comment on the factors that affect the choice of the use of continuous epidural versus local anesthesia in the cesarean group, particularly with reference to the significance of coagulation defects that may occur in the pregnancy-induced hypertensive patient.

Dr. Robert Goodlin, Omaha, Nebraska. This is a much-needed report. This, I believe, is the first to report that the incidence of abnormal fetal heart rate patterns are not higher in parturients with epidural anesthesia than in those with nonepidural anesthesia.

In Omaha we are behind the rest of the country and now are beginning to have our first malpractice suits in obstetrics. The local anesthesiologists have asked that we no longer request epidural anesthesia for cesarean section because they cannot use Marcaine because of its cardiac problems, Nesacaine because of its nerve effects, and Lidocaine because too much drug is required. I wonder what will be the fate of obstetric epidural anesthesia in California? The third question I have concerns the estimate of plasma volume in the laboring patient. My experience suggests that for accuracy the plasma volume should be measured. We found that at least a third of patients with preeclampsia had normal or elevated plasma volumes. Dr. Joyce (Houston) has had wide experience with this problem and with central venous pressure monitoring and uses normal saline solution to expand plasma volume. I have recommended 5% albumin of hetastarch. My fourth question is What fluids does the author's institution use to expand plasma volume?

Dr. Resnik (Closing). I am glad to confirm your prejudices—they were ours also and that is why we did the study. First, Dr. Nelson, I would like to acknowledge your concern about use of retrospectively collected data for such a study. As to length of labor, I would point out that the etiology for the lengths of such labors may be multifactorial. The British have demonstrated in several good prospective studies that the length of the second stage is prolonged with use of epidural anesthetics. I must say I am not personally too surprised about that.

Dr. Moyers, it was generally the patient's choice of local versus epidural anesthesia. Occasionally the choice of anesthetic was mandated because of the severity of the disease or some other mitigating factor. Epidural anesthesia was avoided in patients who had increased bleeding times or platelet counts of <50,000.

Dr. Goodlin, we used lactated Ringer's solution only for plasma volume expansion, and we had no specific measurements for plasma volume.

The significance of meconium in midtrimester genetic amniocentesis

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Since the advent in recent years of midtrimester amniocentesis for genetic testing, there has been an increasing number of reports of occasional instances of meconium-stained amniotic fluid of uncertain prognostic significance. Previous reports have suggested a fetal mortality of 30%. With larger series now available for study, more accurate information on the incidence of this occurrence and its significance is presented. The present series consists of 4709 consecutive amniocenteses performed from 1978 to 1983, at two genetic testing centers in Portland, Oregon. Meconium-stained amniotic fluid was found in 79 cases, for an incidence of 1.67%. Contrary to previously published reports, the fetal mortality was 5.06%. Thus the finding of meconium-stained amniotic fluid during midtrimester genetic amniocentesis may not carry the ominous prognosis that originally might have been predicted. (AM J OBSTET GYNECOL 1985;152:413-7.)

Key words: Midtrimester amniocentesis, meconium, genetic testing

Midtrimester amniocentesis for prenatal genetic diagnosis has been performed since 1967.[1] Since then, there have been a few scattered reports in the literature of the finding of meconium staining of the amniotic fluid, usually from relatively small series. Karp and Schiller[2] reported on this phenomenon in 1977, and concluded that this finding was of little significance. This was in contrast to a subsequent report[3] which noted a fetal loss of 30%. Subsequent reports by Golbus et al.,[4] Crandall et al.,[5] and Cruikshank et al.[6] have confirmed high perinatal mortality with discolored amniotic fluid. However, those studies included fluid discolored by blood as well as by meconium. An additional study from Australia on a small number of cases did not indicate a poor prognosis.[7]

Midtrimester amniocentesis for prenatal diagnosis has now become an accepted standard of practice in most communities. In the present study, I evaluated 4709 consecutive midtrimester genetic amniocenteses from 1978 to 1983, in order to develop reliable figures for counseling in regard to spontaneous abortion. I thought that a larger series would help to clarify the prognostic significance.

Material and methods

All of the amniocenteses in this study were performed on patients in the prenatal diagnosis centers at two institutions in a large metropolitan area. These patients included those referred from throughout the Pacific Northwest region. From 1978 to 1983, 2946 consecutive amniocenteses were performed at the Oregon Health Sciences University, and an additional 1763 consecutive amniocenteses were performed at the Emanuel Hospital Perinatal Center, Portland, Oregon, from 1981 to 1983.

Each patient had an ultrasound examination to confirm gestational dates, placental localization, and multiple gestation or anomalies. A routine protocol for sterile amniocentesis with a No. 22 spinal needle was followed. Real-time ultrasound was used for guidance of the needle, and fetal heart tones were monitored. Initially, most of the samples of amniotic fluid were analyzed by spectrophotometric scanning, and the color of the fluid was recorded for all. Only cases noted specifically to have meconium or those in which the amniotic fluid had a greenish tinge were included in the final results. Amniotic fluid noted to be brownish or blood-tinged was excluded.

The patient's age, parity, gestational age, pertinent past history, chromosomal result, and perinatal outcome were also recorded. All amniotic fluid was subjected to cytogenetic study and analysis for α-fetoprotein.

Results

At the two institutions involved in the study, 4709 consecutive amniocenteses were performed, 79 of which showed meconium-stained amniotic fluid. This was an incidence of 1.67%, which is in line with previously reported incidences of one in 40, one in 50, and one in 52.[2, 3, 7] Table I shows the number of amniocenteses with meconium-stained amniotic fluid, by year. Among the 79 cases in which the amniotic fluid was

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Table I. No. of amniocenteses by year and institution

Year	*Amniocenteses at Oregon Health Sciences University*	*Meconium-stained amniotic fluid*	*Amniocenteses at Emanuel Hospital*	*Meconium-stained amniotic fluid*	*Spontaneous abortion*	*Total*
1978	394	11				11/394
1979	533	14			1	14/533
1980	644	12				12/644
1981	618	8	195	1	1	9/813
1982	309	6	658	15	1	21/967
1983	448	4	910	8	1	12/1358
Total	2946	55	1763	24	4	79/4709

Table II. Indication for amniocentesis in those with meconium-stained amniotic fluid

	Meconium-stained amniotic fluid						
Indication	*1978*	*1979*	*1980*	*1981*	*1982*	*1983*	*Total*
Maternal age (yr)	11	12	12	5	19	10	69
Previous child with anomaly	0	2	0	4	0	1	7
Anomaly in other family member	0	0	0	0	2	0	2
Social (drug ingestion)	0	0	0	0	0	1	1
							79

found to be stained with meconium, there were four instances of fetal death (including one fetus with a chromosomal anomaly that was therapeutically aborted), for a neonatal mortality of 5.06%. Thus this incidence is much lower than that previously reported in the initial study.

Most amniocenteses with meconium-stained amniotic fluid (69 of 79) were performed for maternal age of 34 years or older (see Table II). The ages of the patients in this group ranged from 34 to 43 years. Seven amniocenteses were performed because of a past history of an infant with a congenital anomaly, and two were performed because of a family history of congenital anomaly. One amniocentesis was performed in a 21-year-old woman who was a cocaine abuser.

There were four sets of twins with meconium-stained amniotic fluid. In two of these, both amniotic sacs contained meconium-stained fluid; in the other two, each had one sac with clear fluid and one with meconium. One of these later became a case of fetal death (see Table III).

There was no correlation between the degree of meconium-stained amniotic fluid and fetal outcome. In all instances in which the meconium-stained amniotic fluid was described as "dark meconium," "thick meconium," or "dark green," the outcome was a normal birth.

Comment

The appearance of meconium-stained amniotic fluid has always been associated with significant neonatal morbidity. Since the advent of amniocentesis for prenatal diagnosis, it is apparent that occasionally meconium will be present in the midtrimester. This report and others have shown that this will occur between 1% and 2% of the time. What has not been clear is whether this early appearance of meconium is an indication of early fetal distress and subsequent poor perinatal outcome. An earlier study in this institution reported a mortality rate of 30% (three cases of fetal death among 10 cases with midtrimester meconium).[3] It was also concluded that when these cases were added to the only other study reported in the literature, the fetal mortality rate approximated 20%.[2] A later report by Cruikshank et al.[6] found a 29% mortality rate with "discolored" fluid. Those authors reported 17 cases among 923 amniocenteses. However, only nine of the 17 had green or meconium-stained amniotic fluid. The other eight had "mahogany" or brown amniotic fluid, which undoubtedly reflected blood rather than meconium. Thus, even when those cases that revealed blood rather than meconium are excluded, a significant mortality rate still remains. In this study, I excluded all cases in which the amniotic fluid was described as "brown" or "blood-tinged," or was any other questionable color. This evaluation does depend to some extent on observer subjectivity when the amniotic tap is done, but most of the samples of amniotic fluid were analyzed spectrophotometrically.

One encouraging study in the literature was reported from Australia in 1981.[7] It cited 10 cases of meconium-stained amniotic fluid in 520 consecutive amniocenteses, with no instances of fetal death. Svigos et al.[7] thought that the previous study by King et al.[3] may have been influenced by the finding that in two of the three cases of fetal death the α-fetoprotein was elevated also. Moreover, the study by Karp and Schiller[2] con-

Table III. Cases of fetal death

Patient	*Maternal age (yr)*	*Gravidity*	*Parity*	*Gestational age (wk)*	*History*	*Amniotic fluid*	*Results*	*Outcome*
E. S. (Oregon Health Sciences University), 8/79	38	7	5	16	Abortus 2	Moderate meconium	46,XY	Spontaneous abortion after amniocentesis
P. B. (Oregon Health Sciences University), 2/81	21	2	0	18	Abortus 1	Green	45,X (ultrasound = gross anomaly)	Therapeutic abortion
N. M. (Oregon Health Sciences University), 3/82	35	2	0	14	0	Both meconium	Twins, 46,XY	Twin A—Death Twin B—Normal
B. N. (Emanuel Hospital), 2/83	34	1	0	15.6	0	Green	46,XX	Abruptio placentae at 22 wk, died at 1 hour

tained cases in which previous amniotic fluid taps had been unsuccessful, and cases with threatened abortion. The question of blood versus meconium also enters again here.

All of the previous studies were limited by a small number of samples, necessitated by a low incidence of occurrence of meconium. However, during the past 5-year period, 1978 to 1983, I have now been able to review 4709 consecutive amniocenteses. Among this large number, only 79 instances of meconium-stained amniotic fluid were noted. There were only four cases of fetal death in this study (5.06%), including one instance of therapeutic termination of the pregnancy. Thus, a larger number of cases has provided a more accurate picture of the true prognostic significance. It is apparent that the prospect of impending fetal death is not nearly so great as was once feared.

The reasons for the appearance of meconium in the midtrimester remain unclear, however, and it is likely that the causes are multiple. Karp and Schiller postulated that their observation of meconium was related to some transient fetal stress, i.e., first-trimester bleeding. However, almost no instances of such an occurrence were observed in the present sample. It should also be noted that the presence of meconium in the midtrimester may indeed be transient, inasmuch as most patients in this study had clear fluid at the time of delivery. Since the patients in this study underwent delivery at many different hospitals in a four-state area, it was virtually impossible to obtain accurate records that stated the color of the amniotic fluid at the time of delivery. There were also cases of fetal distress with meconium at delivery which undoubtedly were related to third-trimester or labor-and-delivery complications, and were not related to the earlier presence of meconium in the second trimester.

Previous studies have concluded that additional follow-up with larger numbers were needed. It is hoped that this study will offer some reassurance that the presence of meconium in the midtrimester does not necessarily portend a poor outcome. Instead, the prognosis is quite favorable.

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Discussion

DR. RICHARD A. BASHORE, Los Angeles, California. Dr. Allen has presented an interesting analysis of 4709 midtrimester genetic amniocenteses in which meconium staining of the amniotic fluid was associated with a 5% fetal mortality rate. He has compared his findings with those of previous studies in which a perinatal mortality rate as high as 30% was noted in association with meconium staining of amniotic fluid. On the basis of a comparison of these results, he concluded that the finding of meconium in amniotic fluid at the time of genetic amniocentesis was not so ominous as originally reported. He attributed the differences in perinatal mortality rates to the availability of larger series for study, and to more accurate information in regard to the true incidence of meconium staining.

Discoloration of amniotic fluid may be caused by the presence of meconium, blood or blood pigments, or bilirubin, or any combination of the three. Although the gross appearance of discolored amniotic fluid may

Table I. Selected information contained in reports cited by Dr. Allen

Study	*Patients*	*Abnormal amniotic fluid*	*Spectrophotometric analysis*	*Abnormal α-fetoprotein*	*Prior bleeding*	*No cell growth*	*Missed abortion*	*Outcome*	
								Fetal death	*Normal*
Karp and Schiller[2]	234	6 (2.5%)	Yes	—	3	0	0	0	6
King et al.[3]	514	10 (1.9%)	Partial	3	3	3	0	3	7
Golbus et al.[4]	3000	36 (1.2%)	Yes	7	—	6	9	12 (3 Therapeutic abortions)	24
Crandall et al.[5]	2000	22 (1.1%)	No	—	15	—	—	3 (2 Therapeutic abortions)	19
Cruikshank et al.[6]	923	17 (1.8%)	No	1	—	—	3	5	12
Svigos et al.[7]	520	10 (1.9%)	Yes	0	3	0	0	0	10
Allen (present report)	4709	79 (1.7%)	Partial	0	—	0	0	4 (1 Therapeutic abortion)	75

References are those cited by Dr. Allen.

suggest the presence of meconium, spectrophotometric analysis of the fluid is widely accepted as an appropriate method for determining whether discoloration is, in fact, due to meconium or to other pigments. Dr. Allen has stated that, initially, most of the samples of amniotic fluid were analyzed by spectrophotometry, and the color of the fluid was recorded for all specimens. How many of the samples were actually evaluated by spectrophotometry is unclear. Dr. Allen excluded from his study any samples of amniotic fluid which were brownish in color. When samples with similar brown discoloration were analyzed by spectrophotometry by the other investigators cited by Dr. Allen, they reported large peaks at 405 and 415 mμ that indicated meconium and blood pigment.

However, if we assume that in most instances the discoloration of amniotic fluid noted in these studies was due to meconium, the combined data (Table I) can be interpreted in a way that will provide a more precise depiction of the prognostic significance of meconium in second-trimester amniotic fluid. For instance, the inclusion of "missed abortions" among fetal deaths reported in the earlier studies and the prognostic significance of meconium in these cases should be clarified. Genetic amniocentesis was performed after fetal death because of the lack of real-time ultrasound capability in the early phases of these studies. With present technology, genetic amniocentesis would usually not be performed in the absence of fetal cardiac activity. However, if amniocentesis is performed after fetal death, for whatever reason, such cases should be excluded from the interpretation of the prognostic significance of meconium staining. Although prior vaginal bleeding occurred rather frequently in some of the series noted, a history of it had very little relationship to the prognostic significance of meconium. In only one case in the combined studies did a history of prior vaginal bleeding and the presence of meconium precede fetal death. In the remainder of the cases with a history of vaginal bleeding and meconium in amniotic fluid, fetal outcome was normal. However, when meconium staining of amniotic fluid was accompanied by abnormal levels of α-fetoprotein, failure of cell growth in culture, or congenital anomalies, the fetal mortality rate for the combined series was 66% (10 of the 15 fetal deaths), if missed abortions are excluded from the analysis. When meconium was present as an isolated finding, the fetal mortality rate was 3% (five fetal deaths among 153 patients with meconium).

When the information from these studies is interpreted in this manner, two groups of patients can be identified, each associated with a distinctly different prognostic outlook with meconium staining. If one or more of the abnormalities just described was present in association with meconium, a very high rate of fetal mortality occurred. If no other abnormalities were present, the fetal mortality rate was not unusual for the age of the population involved. The appearance of meconium in this group of patients probably reflected transient fetal distress, as indicated by the fact that, when such cases were followed to term, the amniotic fluid was clear at the time of delivery. On the basis of this interpretation, it would appear that the presence of meconium in amniotic fluid at the time of second-trimester genetic amniocentesis must be viewed in relationship to other variables, if its real prognostic significance is to be determined.

Dr. Frederick Hanson, Davis, California. We have had a little different experience and I would like to comment on that. We recently collated our data, and I happen to have a few slides that I would like to show. We have looked at more than 2000 of our patients and found essentially the same number of samples of discolored amniotic fluid but twice the fetal mortality rate and a high incidence of adverse outcome. I am unable to account for the difference between our two studies.

We experienced no difficulty in cell growth and, certainly, the vast majority of pregnancies ultimately had a normal outcome. However, we have seen an approximately eightfold increase in the mortality rate when compared to that with fluid of normal color.

You can see from this first slide that at least two thirds of the mortalities occurred in patients who had some history of bleeding and/or cramping prior to their amniocenteses. We found a total loss rate in this group of about 13.5% and an abnormal fetal outcome of slightly over 25%.

I might comment on one of Dr. Bashore's statements. In our genetic program, we believe very strongly that, regardless of whether the fetus is dead or alive (and we see about 40 unanticipated fetal deaths per year in our patients prior to amniocentesis), an amniocentesis should be performed on those patients. Much valuable information can be obtained for assisting patients in subsequent counseling sessions if further pregnancies are desired.

I would like to ask whether the group in Portland has made any attempt to identify what is coloring the amniotic fluid. We have performed the usual spectrophotometric analysis and it has shown the usual peak between 400 and 410 nm in all these samples of fluid. We have taken it a step further and have some interesting data. I stopped sending the samples of fluid for spectrophotometric analysis and we subject them to polyacrylamide gel electrophoresis. We see two different groups of patients. None of our patients has been tapped previously. Those with brown fluid have a band that migrates with fetal hemoglobin. Those with greenish fluid have a band that migrates with material that we have obtained from the fetal gastrointestinal tracts of midtrimester prostaglandin abortuses.

Dr. Robert Resnik, San Diego, California. I was interested in hearing Dr. Hanson's point about their polyacrylamide gel studies. The peaks for oxyhemoglobin and meconium are so close that with spectrophotometric analysis it is very difficult to distinguish the two. There is some question of whether the fetus is capable of passing meconium or making meconium that early in gestation (at least in terms of what we consider meconium to be). There is an intestinal polypeptide called motalin which is known to be responsible for intestinal peristalsis in the fetus. In the course of fetal development, motalin does not appear until about 30 weeks' gestation. An interesting study was reported in *Lancet* 4 years ago which compared umbilical cord levels of motalin in term babies delivered by elective repeat cesarean section with levels in babies who had fetal distress; the same was done in premature babies, except not in elective repeat cesarean sections. Premature babies were delivered with and without fetal distress. The very low–birth weight baby—30 weeks or less—does not make motalin, and is very rarely reported to produce "meconium" and maybe some oxyhemoglobin pigment. I should like to ask whether you think you are dealing with meconium or if these are "brown-green fluids" and, if they are not, should they be evaluated any more thoroughly or just be called "brown-green fluids." I am not sure we know exactly what that is.

Dr. Allen (Closing). Dr. Bashore, as to your question about why we did not analyze all of these samples of amniotic fluid spectrophotometrically, it was my impression initially that all of them were so analyzed. However, in talking to the two physicians who were in charge of both of these programs, they were so confident that they were getting meconium on these later taps that they did not submit these fluids for spectrophotometric analysis, as Dr. Hanson has pointed out that he does at his institution at Davis. That is why the figure is not 100%, but I would say that probably more than 90% were submitted for spectrophotometric analysis. As to why we get fewer mortalities than what Dr. Hanson had at Davis, I do not have a real answer for that. I noticed that 8.2% of your series were premature babies, one of the really large factors in the mortality rates. This may not be related to transient fetal stress, first-trimester bleeding, or whatever it is that is going to produce the discolored or meconium-stained fluid. We have not tried to test the fluid for meconium per se. As I stated earlier, I think that the people involved are confident that they are looking at meconium. In the study from Dallas,[1] those investigators did test meconium fluid, and tests were run for intestinal disaccharides and intestinal alkaline phosphatase. This fluid did test out definitely as meconium rather than blood; however, the conclusion was that it did not make any difference whether they called it blood or meconium. It was still discolored fluid. Also, meconium does seem to be a normal physiologic finding in midpregnancy.[2] That is the same answer therefore to Dr. Resnik's question. Other than spectrophotometry, we have not specifically tested for meconium, although we are certain that what we were looking at was meconium, but whether it was or was not, it does not seem to have the ominous prognostic significance that we once worried about. The important part is that the earlier concern about the poor prognosis, because of our concern about the presence of meconium being an ominous sign, has been lessened. We would rather have clear fluid than discolored fluid. It does not have the ominous prognosis that we once believed.

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Human lymphoblastoid interferon in the treatment of advanced epithelial ovarian malignancies: A Gynecologic Oncology Group study

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The purpose of this study was to evaluate the toxicity and antitumor activity of low doses of human lymphoblastoid interferon in 36 patients with measurable disease in whom higher priority treatment methods had failed. All but one had surgically confirmed advanced disease and had undergone initial treatment with a multiagent chemotherapeutic regimen in combination with cisplatin; four patients had also received radiation therapy. Their age range was 28 to 74 years. All had Gynecologic Oncology Group performance grade 2 or better (Karnofsky, 50% and above). Human lymphoblastoid interferon was administered at 5 megaunits/m^2 intramuscularly, for 5 days per week (Monday through Friday) for 6 consecutive weeks. Patients who exhibited response or stable disease at 6 weeks were placed on a regimen of maintenance therapy at the same dose level for 2 days per week (Monday and Tuesday), for up to 12 months or until progression. Twenty-eight patients were evaluable for response: two with complete responses (7.1%), three with partial responses (10.8%), 14 with stable disease (50.0%), and nine with increasing disease (32.0%). Among the cumulative adverse effects, fatigue was most common, followed by moderate leukopenia and thrombocytopenia. Other observed adverse effects consisted of severe nephrotoxicity in two patients and myocardial infarction in one patient. It appears that therapy with human lymphoblastoid interferon may have cytostatic and possibly cytotoxic effects in this group of patients, with acceptable adverse reactions. (AM J OBSTET GYNECOL 1985;152:418-23.)

Key words: Ovarian carcinoma, human lymphoblastoid interferon, therapy

First-line combination chemotherapy for advanced epithelial ovarian carcinoma subsequent to aggressive surgical debulking has induced a high remission rate; however, the 5-year survival rate has not as yet improved dramatically. Furthermore, in patients in whom it is not possible to induce remission with first-line therapy or in whom progression is noted after remission, the second-line treatment options are limited and response rates are usually low. Other factors which make attractive the study of the use of interferon as a biologic response modifier in this disease are: (1) possibility of tumor-associated antigens with ovarian tumors[1-3]; (2) suggested improved survival when a nonspecific immune stimulant bacille Calmette Guérin vaccine has been used along with combination chemotherapy[4]; (3) investigations in other malignancies showing antitumor activity of interferon[5]; and (4) in vitro and in vivo early evidence of effectiveness of interferon against ovarian carcinoma.[7-9]

The interferons are now better understood cellular glycoproteins, divided into three types (α-, β-, and γ-interferons) and many more subtypes on the basis of their antigenic properties; the α-interferons are produced from leukocytes or lymphoblasts, the β-interferons from fibroblasts, and γ-interferons from T cells. The α- and β-interferons are now being produced in large quantities, thus allowing the evaluation of their clinical value. The properties of interferon are antiviral, antiproliferative, and immune-modulating. These effects are believed to be executed by binding to cell-surface receptors, and the cell-surface receptor is monitored by chromosome 21. The intracellular mechanism of action appears to be through induction of several enzyme systems.

Clinical trials with interferon have included viral infections (human papilloma virus and herpes zoster) and

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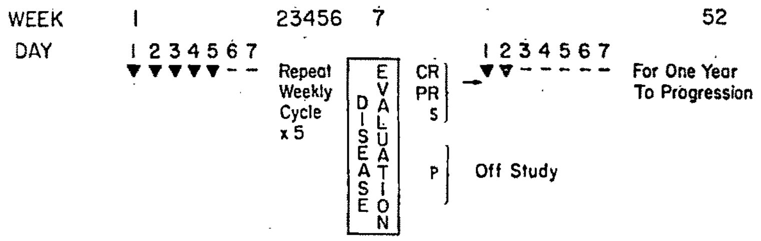

Fig. 1. Dose and schedule of interferon therapy. ▼ = interferon, 5 megaunits/m² intramuscularly. CR = complete response; PR = partial response; S = stable disease; P = progression.

malignancies, such as osteogenic sarcoma, breast cancer, renal cell adenocarcinoma, melanoma, leukemia, lymphoma, myeloma, and many others.[6]

Human interferon has been previously tested against epithelial ovarian tumors both in vivo and in vitro. Sensitivity of ovarian carcinoma cells to interferon assessed in vitro with the use of semisolid agar techniques suggests a significant response by observations of reductions in tumor cell colony counts in five of seven cultures.[7] Clinical studies to assess the value of human interferon in ovarian epithelial cancer have been sporadic but consistently suggest biologic activity, especially in a few cases in which malignant effusions were the measurement of response.[8, 9] These reports also have suggested clinical "responses" which have not met the standard criteria of complete or partial responses; in some patients who were noted to have stable disease, prolonged progression-free intervals have been observed.[8, 10]

The main goals of the present study were to study the antitumor activity and associated adverse effects of therapy with human lymphoblastoid interferon in patients with advanced or recurrent epithelial ovarian malignancies and also to assess the clinical response rate to low doses of human lymphoblastoid interferon (<10 megaunits/m²) in those patients with ovarian cancer in whom high-priority treatment methods had failed.

Material and methods

Selection of patients. Eligibility criteria required all patients to have: (1) histologically confirmed advanced or persistent epithelial ovarian carcinoma; (2) measurable disease by palpation or radiologic study; (3) only one prior cisplatin-containing chemotherapeutic regimen or radiation therapy, wherein no more than 30% of bone marrow had been exposed; (4) Gynecologic Oncology Group performance of grade 2 or better (Karnofsky, 50% or better); (5) no other previous or concomitant malignancies, except nonmelanoma skin neoplasms and all the intraepithelial lesions; (6) no major organ malfunction; (7) a signed informed-consent form. Provision was made for accepting up to three patients on study who had refused to receive more proved modalities of treatment.

Interferon. Human lymphoblastoid interferon (Wellferon, Burroughs Wellcome, Research Triangle Park, North Carolina) was used in this study. This is an α-type of interferon derived from the Namalwa cell line (Burkitt's lymphoma) by viral induction, Cantell's technique.[11] It is isolated, concentrated, and purified from cell-free supernatants to 95% purity. Human lymphoblastoid interferon has been purified to a level of 2 × 10⁸ international units of human α-interferon per milligram of protein. The biologic activity of Wellferon is expressed in megaunits, where 10⁶ IU equal 1 megaunit. This unitage is determined in a viral cytopathic effect inhibition assay standardized against the international α-interferon standard 69/19. Extensive experimental work has demonstrated that Wellferon is nearly identical in its chemical, physical, immunologic, and biologic properties to interferon derived from buffy coat cells of human blood. It contains at least 12 human α-interferon subtypes.

Dose and schedule. This treatment had an induction phase of 6 weeks, during which time interferon was given for 5 weekdays, with 2 days off. The intramuscular dose was 5 megaunits/m². Patients were hospitalized for the first few days of treatment for close observation, as well as to teach them self-administration of the therapy. The outpatient follow-up was weekly during the induction phase for observation of toxicity. As noted in Fig. 1, at the conclusion of the induction phase, patients who had shown a response or maintenance of stable disease went on a regimen of maintenance therapy at the same dose level, 2 days on and 5 days off. Subsequent follow-up was every 3 weeks or more often if needed. The maintenance therapy was continued for 52 weeks or until progression. During the induction or maintenance phases, no escalation of doses was allowed, other than modifications for toxicity, with incremental escalation again after recovery from toxicity. Observations and studies included regular physical examinations, assessment of performance status, periodic hematologic and blood chemistry panels, as well as radiologic studies, as deemed necessary.

Response. Tumor response was categorized as complete when total regression of measured tumor was noted and as partial when >50% tumor regression was noted for a minimum duration of 1 month. Patients were considered to have stable disease when tumor regression was <50% or the increase was <25% and to have increasing disease when an increase >25% in measurable tumor was noted or a new lesion was found within 2 months of entry into the study.

Results

Among 36 patients entered into the study, six were excluded because of wrong diagnosis of primaries (three) and improper preprotocol treatment regimens (three). Two patients could not be evaluated for a response, since both had received only 1 week of treatment. Twenty-eight patients could be evaluated forresponses. Two patients showed complete responses (7.1%), three patients showed partial responses (10.8%), 14 patients demonstrated stable disease (50.0%), and in nine patients (32.0%) disease continued to progress during therapy.

The following case reports provide details on the two patients who showed complete clinical response.

Case reports

Case 1. A 52-year-old woman with a Stage III, grade 2 carcinoma of the ovary had been originally treated by operation and combination chemotherapy that contained cisplatin. Approximately 2 years after the initial diagnosis, recurrent pelvic disease was noted. Interferon therapy was initiated at a 7.7 megaunit dose in accordance with the treatment schedule. The pelvic disease (4 by 5 cm) showed evidence of regression by the fifth week of induction therapy, and complete response by the sixth week of maintenance therapy. During the maintenance period, a mild degree of fever and fatigue was noted, along with anorexia and some loss of weight and a moderate elevation of serum glutamic oxaloacetic transaminase. A dose modification was necessary at the second week of the induction phase and again at the sixteenth week of maintenance therapy, because of elevated serum glutamic oxaloacetic transaminase. The performance grade remained the same throughout the course of treatment. The patient, having maintained complete response status for 24 weeks, remained on a regimen of maintenance therapy until recurrent disease was noted. Subsequent to this therapy the patient is alive with disseminated disease and is receiving no further therapy.

Case 2. A 32-year-old woman with Stage III, grade 1 serous cystadenocarcinoma of the ovary had undergone surgical exploration for bilateral pelvic masses; the surgical therapy left gross residual disease in the pelvis. At approximately 6 postoperative weeks, measurable cul-de-sac disease (2 by 2 cm) was noted on the initial referral visit. The patient had refused conventional therapy. Interferon therapy was initiated at 7.20 megaunits in accordance with the treatment schedule. Response to therapy was noted by the sixth week of induction therapy. Continuous resolution of the tumor was observed and complete response status was noted by the tenth week of maintenance. The patient had a complete clinical response throughout 1 year of maintenance therapy and underwent a second-look procedure. No macroscopic disease was present, but microscopically documented residual disease was found intro-abdominally and also in the retroperitoneal lymph nodes. The adverse effects observed during this course of treatment were mild degrees of fever, chills, and headaches. Elevations of total bilirubin, serum glutamic oxaloacetic transaminase, and alkaline phosphatase were noted to be minimal and resolved by the sixth week of maintenance therapy. While on a regimen of maintenance therapy, the patient experienced severe fatigue that required dose modification. Renewed escalation of dosage was not possible. During the course of the study the performance grade remained the same. Currently, the patient has remained free of clinically measurable disease for a duration of 26 weeks after discontinuation of interferon therapy, and has continued to refuse other treatment.

Partial responses were noted in three patients whose age range was 28 to 63 years. Two patients had well-differentiated serous cystadenocarcinoma, and one had poor differentiation. All had measurable pelvic disease, and one also had a histologically confirmed mediastinal nodule. The partial responses were noted within 6 to 7 weeks from onset of therapy and were confirmed by physical examinations as well as by computerized tomographic scan of the mediastinal nodule, which later regressed completely. The responses lasted for 34, 39, and 52 weeks. The side effects of therapy were mild to moderate, although severe fatigue was seen in two and severe thrombocytopenia was seen in one, all of which required modification of dosages. Two patients were alive at 12 and 17 weeks after discontinuation of interferon therapy, and the third patient died of disease 5 weeks thereafter.

In 14 of 28 patients who could be evaluated, disease was stable at the conclusion of the induction phase of therapy. Their age range was 37 to 74 years (median, 58 years). All patients had undergone intitial surgical therapy and subsequently were treated with combination chemotherapy that contained cisplatin. Three patients also received pelvic irradiation in addition to chemotherapy. Sites of recurrence were pelvic (10 patients), abdominal (one patient), and distant (three patients). All 14 patients had epithelial carcinoma, grade 2 differentiation in five and grade 3 in nine. The duration of stable disease ranged from 8 to 52 weeks (median, 22 weeks). Ten patients who died of disease were on a regimen of maintenance therapy for a range of 6 to 34 weeks (median, 13 weeks). Death was noted within 2 to 28 weeks (median, 8 weeks) after progression during interferon therapy. Four patients who remain alive with disease were on a regimen of maintenance therapy for a range of 19 to 52 weeks (median, 33 weeks) until progression of disease. They remain

Table I. Major side effects of interferon therapy

	Adverse effects							
Grade	*Platelets*	*White blood cells*	*Gastrointestinal*	*Renal*	*Serum glutamic oxaloacetic transaminase*	*Chills, fever*	*Fatigue, malaise*	*Headache*
0	12	10	15	18	14	8	10	21
1	8	3	4	10	13	12	8	6
2	9	12	11	0	3	7	7	3
3	1	5	0	2	0	3	5	0
4	0	0	0	0	0	0	0	0
Total	30	30	30	30	30	30	30	30

alive with disease, after interferon therapy, for 12, 13, 34, and 52 weeks.

Nine of 28 patients who were evaluated showed evidence of increasing disease during induction therapy. Site of measurable disease was the pelvis in four, the abdomen in three, and distant in two. Eight patients had received combination chemotherapy, and one patient, whole-pelvis radiation therapy. The histologic tumor differentiation was grade 2 in two patients and grade 3 in six patients, and was not specified in one patient. This is the only group of patients in whom grade 2 performance status was recorded at entry (in four of nine cases). The time interval to progression was noted to be 2 to 6 weeks (median, 5 weeks). All of these patients subsequently died of disease, within 1 to 33 weeks (median, 2 weeks).

Adverse effects. Adverse effects were categorized according to standard Gynecologic Oncology Group criteria, on the basis of the intensity of symptoms, multiples, or degree of suppression of normal values. Furthermore, they were classified as acute and cumulative (Table I). During the induction phase, the acute adverse effects, which were related to dosage, were fever, chills, and flulike symptoms. These were noted in 22 of 30 patients in varying degrees, with the majority having effects that were mild or moderate in intensity, and only three having severe effects. The intensity appeared to decrease with continued exposure. The cumulative adverse effects, which were totally dependent on dosage, were primarily chronic fatigue and hematologic side effects. Leukopenia was noted in 18 patients (median nadir, 2500; range, 1200 to 3100); in five of these the condition was severe and required modification of dosage. Thrombocytopenia was observed in 16 patients, in one of whom it was severe and required adjustment of dosage (median nadir, 79,500; range, 45,000 to 144,000). The other adverse effects were gastrointestinal, headaches, and elevation of serum glutamic oxaloacetic transaminase and alkaline phosphatase, none of which was severe. Renal toxicity, exhibited as elevation of blood urea nitrogen and creatinine, was found to be mild in 10 patients and severe in two; in the latter it was suspected to be a preexisting condition secondary to previous nephrotoxic chemotherapeutic agents. Adverse effects during maintenance therapy were milder and less troublesome to the patients; however, modification of dosage was required in three patients because of severe fatigue (in two) and severe thrombocytopenia (in one). No other major organ toxicity was found throughout the course of this study. One patient who had a history of cardiac disease was admitted to the intensive care unit at the fifth week of interferon maintenance therapy with massive myocardial infarction and died.

Comment

The early reported studies in which interferon was used for treatment of various malignant conditions were tainted with multiple problems, e.g., lack of sufficient drug for adequate evaluation, low purity of harvested interferon, patient populations with heavy previous treatments, and performance status not uniformly reported. Lack of understanding of dosage and scheduling was also a variable. Although some of the above-mentioned problems remain even in current studies, significant progress has been made. In spite of the above-mentioned problems, multiple studies have proved the antiviral properties of interferon, and other studies strongly suggest its antiproliferative biologic activity in many tumors. The use of it in ovarian tumors has been limited to recent times, and few studies have been reported. These studies have been small, dosage schedules have varied, and routes of administration have differed.

Several patients with malignant pleural and abdominal effusions have shown a response, as reported by Einhorn et al.[8] and Hill et al.[13] Partial or minimal responses were also reported in these two studies. Freedman et al.[10] and Silver et al.[12] also reported on a group of patients in whom disease remained stable for longer durations than expected. The dosages which were generally lower than those used for other tumors, ranged from 1 × 10^6 to 10 × 10^6 IU.

In this study, we entered 28 patients with human lymphoblastoid interferon therapy who could be evaluated and in whom pretreatment background and other conditions met certain criteria to achieve scientifically acceptable uniformity. The overall complete and partial response rate was 17.9%, and the median progression-free interval for responders was 41 weeks. The 14 patients in whom stable disease status was achieved represent an interesting segment of the study population, for they make up 50% of the study group; they had a median progression-free interval of 21 weeks. Four of the 14 patients with stable disease have remained alive with disease for 12, 13, 34, and 52 weeks after progression with interferon therapy. The 10 patients who died of disease after a stable disease status was maintained for a median of 16.6 weeks were alive for a short 9.9 weeks, on the average, after the cessation of therapy.

Of the 36 patients entered into the study, 30 could be evaluated for toxicity. The adverse effects observed were dose-related acute toxicities of fever, chills, and flulike syndrome in 22 of the 30; in only three were these conditions severe. Dose-limiting toxicities were: (1) chronic fatigue or malaise in 20 of the 30 patients (severe enough to require modification of dosage in five); (2) hematologic conditions (leukopenia was moderate and thrombocytopenia was mild overall, except in one patient in whom it was life-threatening); and (3) transient and mild enzymatic abnormalities (serum glutamic oxaloacetic transaminase and alkaline phosphatase).

In summary, human lymphoblastoid interferon was found to have some biologic activity against advanced epithelial ovarian cancer in a study of 28 patients who had measurable disease and a common background in regard to previous therapy and overall condition. There were 17.8% complete and partial responders. In one half (50%) of the patients who could be evaluated, a period of stable disease that lasted for a median of 22 weeks was achieved. This is noteworthy when compared to the nine patients (32%) who did not respond to therapy and who died of disease within a median of 7 weeks from entry into the study. Although interferon therapy is not free of side effects, most patients had an overall acceptable tolerance. The dose-limiting adverse effects were few and none was life-threatening. These results indicate that human lymphoblastoid interferon (Wellferon) may be well tolerated, and an additional study of its role as an anticancer agent in epithelial ovarian cancer is indicated. An obvious question resulting from these data would be the possible role of interferon in combination with standard cytotoxic chemotherapy in untreated postoperative patients. This role, plus the possible associated adverse effects of combination therapy (multiagent chemotherapy plus human lymphoblastoid interferon), will be the subject of future studies.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. William E. Crisp, Phoenix, Arizona. Immunotherapy started in the late 1800s, when Busch and Coley reported that streptococcal infections caused necrosis in human tumors. This led to the famous Coley's toxins as a nonspecific stimulus to the immune system, with secondary effects on tumors.

The immune system is extremely complex, with both specific immune recognition reactions, mediated either by antibodies or by cells, and secondary nonspecific consequences, which consist of a variety of biologically active substances being released from lymphoid cells that in turn activate a multiplicity of biologic systems.

Clinical immunotherapy exploits both the specific and non-specific reactions of the immune system to destroy malignant cells.

Interferons are one of those "turn on" substances synthesized by many different cells that inhibit intracellular viral replication and also have definite antiproliferation properties. These antitumor properties function in several ways: (1) by augmenting lymphocyte cytotoxic activity, (2) by stimulating machrophage activity, and (3) by increasing the cytotoxic activity of the natural killer cells.[1]

Interferon, with all of these positive in vitro observations, was considered to be the new "magic bullet," but, unfortunately, previous clinical trials were not so convincing, probably because the trials were done in anergic patients with limited immunologic defenses, and, second, because of the impurity of the interferon material.

Recent recombinant DNA methods have now been successfully applied to specific production of interferon and this has led to the discovery of at least 10 molecular variants of subtypes of leukocyte interferon.

When one recognizes all the above-mentioned variables associated with the present study, along with the limited numbers, one has to be encouraged by the results obtained in this group of "end point" patients.

The only technical question concerns the statement that chromosome 21 monitors interferon cell-surface receptors.

My understanding is that the cell-surface receptors for human α-interferon are encoded on chromosome 21. To date, no one knows whether the chromosome "monitors" receptor expression.

It is also of interest to note that the results obtained from this study were almost identical to those in the in vitro studies published by Salmon et al.,[2] at the University of Arizona. Salmon and others[3] have reported that those tumors that are most responsive to interferon are also the tumors that are most sensitive to conventional chemotherapy but then recur after the initial response.

This suggests that either interferon is acting in a manner similar to that of cytotoxic drugs or they have common resistance mechanisms.

Succeeding protocols should probably evaluate the effectiveness of the combined therapy of cyotoxic drugs and interferon.

In almost all of the protocol studies, the one major variable is the immunoincompetence of the cancer patient. If a standard battery of tests (i.e., lymphocyte percentage, percentage of Ia+ cells, percentage suppressor cells, number of helper cells, and the pokeweed mitogen stimulation test[4]) could be used to establish an immunocompetence profile of each patient, the results of the protocol studies would have more statistical significance.

The authors are to be commended for their pioneering efforts that have given us a gleam of hope in the therapy of ovarian carcinoma.

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Dr. DiSaia (Closing). In regard to the question of encoding on chromosome 21, I agree that the monitoring of interferon by chromosome 21 has not been proved, except in the mouse models. It appears that chromosome 16 may be involved in the encoding. Cells isolated from patients with Down syndrome, that are all trisomic for chromosome 21, are more sensitive to interferon. We believe strongly that chromosome 21 has a great influence on the expression of interferon sensitivity. If human chromosome 21 particles are infused into mouse cells that are resistant to interferon, those cells are rendered sensitive to interferon by those particles, but the actual monitoring of interferon by chromosome 21 is yet to be proved.

Twin pregnancy with intrauterine death of one twin

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The antepartum death of one twin is a rare obstetric complication. Two cases are presented, accompanied by a review of the current literature. The premature and neonatal death rates are high in the surviving twins. Toxemia, fetal distress, abnormal presentation, and dystocia are also increased. Maternal disseminated intravascular coagulation has been demonstrated without a concomitant fetal coagulation defect. A more unique finding is fetal disseminated intravascular coagulation with a monochorionic placenta. The common circulation between the live and dead twins may result in fetal cerebral, renal, and cutaneous lesions, usually without demonstrable maternal disease. High-risk obstetric management is reviewed and a careful pediatric follow-up is recommended with monozygotic twins. (AM J OBSTET GYNECOL 1985;152:424-9.)

Key words: Twins, intrauterine death of twin fetus, antepartum death of one twin, retained stillborn twin

Rarely, the antepartum death of one twin will occur in a twin pregnancy. This intrauterine accident occurs in 1:184 twin births, as reported by Ottolenghi-Preti,[1] and was found to be an antepartum complication in seven of 188 monozygotic twin pregnancies in the national Collaborative Perinatal Project.[2] Two cases of antepartum death of one twin occurred at Good Samaritan Hospital, in Corvallis, Oregon, between 1981 and 1983. The incidence of twins for the same period was 1: 85, with 40 sets of twins delivered. The incidence of prematurity was 5.4% of deliveries, and the perinatal death rate was 12.2 per 1000 during the same period.

Case reports

Case 1. A 30-year-old woman, gravida 2, para 0, began prenatal care at 11 weeks' gestation. An obstetric ultrasound examination at 28 weeks' gestation for excessive uterine growth revealed a twin gestation with biparietal diameters of 7.3 and 7.5 cm, separate sacs, and size consistent with gestational age. The ultrasound examination was repeated at 33 weeks' gestation and demonstrated normal interval growth and an oblique lie for the upper twin. The presenting twin had a 6.0 cm biparietal diameter and no cardiac activity. Serum estriol values were obtained at 8 and 4 weeks and at 1 week before delivery, with values of 8.8, 7.4, and 7.6 ng/ml, respectively. The maternal hematologic findings were normal immediately before delivery. Weekly fetal movement tests were started at 30 weeks' gestation and were reactive until 35 weeks. The lack of fetal reactivity of twin B in the presence of a fetal death prompted the decision for delivery. The serum fibrinogen decreased from 530 mg/dl on the evening before delivery to 410 mg/dl on the morning of delivery. The patient was delivered by cesarean section at 35 weeks' gestation. Twin B, in an oblique lie, had a delivery weight of 2580 gm and 1- and 5-minute Apgar scores of 4 and 9. The stillborn fetus weighed 625 gm, and the placenta revealed a velamentous insertion of the umbilical cord and extensive hyalinization. The membranes had a monochorionic-diamniotic configuration.

The live-born twin had transient tachypnea and transient mild hyperbilirubinemia. Urinalysis demonstrated a reaction (3+) to occult blood, but no intact blood cells were seen on microscopic evaluation of the urinary sediment, and renal function studies were normal. The urinary occult blood reaction disappeared before discharge, and the infant was sent home on the eighth day of life. The surviving twin has had normal growth and development and no obvious renal compromise during 2½ years of close follow-up.

Case 2. A 31-year-old woman, gravida 3, para 1, abortus 1, was seen initially at 11 weeks' gestation, and an obstetric ultrasound examination at 25 weeks revealed a twin gestation with an obvious membrane between the twins. The biparietal diameter of the presenting twin was 6.5 cm, with obvious cardiac activity, and fetal measurements were consistent with 25.5 weeks' gestation; however, the second twin had a biparietal diameter of 4.4 cm and no cardiac activity. A baseline coagulation profile and hematologic findings were normal.

Maternal rest was advised and normal progressive fetal growth was noted at 30.5 weeks. At 36.5 weeks' gestation, there was evidence of asymmetric growth of the viable twin and a Grade III placenta.

A repeat clotting profile was normal. Labor began spontaneously on the following day, and a 2245 gm

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Table I. Reported cases of twin pregnancy with intrapartum death of one twin

Author	*Year reported*	*No. of cases*	*Major findings*
Melnick[2]	1977	3	Fetal cerebellar necrosis
Benirschke[3]	1961	1	Fetal renal and cortical necrosis
Durkin et al.[4]	1976	8	Fetal microcephaly, retardation and spasticity
Yoshioka et al.[5]	1979	3	Fetal multicystic encephalomalacia
Moore et al.[6]	1969	3	Fetal renal and cortical necrosis
Livnat et al.[7]	1978	3	Velamentous insertion of cord
Leppert et al.[8]	1979	1	Dystocia
Kerner[9]	1954	1	Delayed passage of fetus papyraceus
Mannino et al.[10]	1977	2	Congenital skin defects
Averback and Wiglesworth[11]	1977	1	Preeclampsia with maternal coagulopathy
Anderson[12]	1957	3	Prematurity
Hainline and Nagey[13]	1982	1	Fetal distress in labor
Hanna and Hill[14]	1984	3	Prematurity, toxemia

Table II. Percentage of all twins complicated by antepartum death of one twin

Author	*Percentage*
Ottolenghi-Preti[1]	0.54
Benirschke[3]	0.5
Hanna and Hill[14]	2.2
Litschsi and Stucki[15]	6.8
Enbom (present report)	5.0

Table III. Velamentous insertion of cord

	No.	*Percentage*
Live-born twin with velamentous insertion of cord	5	20.8
Stillborn twin with velamentous insertion of cord	2	8.3
Normal cord insertion	17	70.9

Data from Melnick,[2] Benirschke,[3] Moore et al.,[6] Leppert et al.,[8] Mannino et al.,[10] Averback and Wiglesworth,[11] Anderson,[12] Hainline and Nagey,[13] and Enbom (present report).

newborn infant with Apgar scores of 8 and 9 at 1 and 5 minutes was delivered. The stillborn fetus weighed 450 gm. Inspection of the placenta showed a monochorionic-diamniotic placenta, with approximately 40% of the surface a fibrotic mass. There was a marginal insertion of the cord on the live-born fetus but no evidence of a velamentous insertion. The fetal cord on the stillborn twin was tightly twisted at the base adjacent to the placental insertion.

The neonate was in the nursery for 2 days with mild hyperbilirubinemia that reached a maximum value of 13 mg/dl. No specific therapy was instituted and the infant was followed as an outpatient with a normal newborn examination. Growth and development have been normal to date.

Comment

A review of the reported cases of intrauterine death of one twin since 1954 reveals the absence of any large individual series (Table I). The frequency of antepartum death of one twin varies from 0.5% to 6.8% of all twin deliveries, as outlined in Table II. An effort to include only antepartum death is attempted in order to remove the multiple other factors surrounding labor, delivery, and intrapartum death.

In evaluating 188 monozygotic twins collected with the national Perinatal Project, Melnick[2] found seven of 188 (3.7%) with antepartum death of one twin. One live-born twin died at 2 months of age of probable disseminated intravascular coagulation and cerebellar lesions. Extrapolating this information gives a disseminated intravascular coagulation/brain damage risk in monozygotic twins of 0.5%, and a random risk of an unborn twin having this serious vascular sequela of one in 600.

The underlying causes for the antepartum death are multiple. Cord accidents are seen more frequently in monochorionic-monoamniotic placentas, especially intertwining of cords.[3] Double survival is a significant feat in itself with monoamniotic twins. Three of four sets of monoamniotic twins presented by Benirschke[3] had significant cord intertwining and/or knotting, which was thought to represent a probable cause of death. The death then sets the stage for more potential harm to the surviving twin. Cord accidents may be precipitated by anomalies of the cord as well. Virgilio and Spangler[16] reported one case and reviewed four cases of twins with antepartum death of one twin and four other cases of singleton delivery with intrauterine death secondary to torsion of the umbilical cord. A common finding was focal absence of Wharton's jelly. The authors concluded that the absence of Wharton's jelly played a role in constriction of the cord and death.

Velamentous insertion of the umbilical cord is also found more frequently with twins. Table III reveals that 29.1% of all twins reviewed had a velamentous

Table IV. Premature birth of live-born twin

	No.	*Percentage*
Mature	17	54.8
Premature	14	45.2

Data from Benirschke,[3] Durkin et al.,[4] Yoshioka et al.,[5] Moore et al.,[6] Livnat et al.,[7] Leppert et al.,[8] Kerner,[9] Mannino et al.,[10] Averback and Wiglesworth,[11] Hainline and Nagey,[13] and Enbom (present report).

Table V. Survival of live-born twin

	No.	*Percentage*
Survived	32	82.1
Deceased (neonatal or infant)	7	17.9

Data from Melnick,[2] Benirschke,[3] Durkin et al.,[4] Yoshioka et al.,[5] Moore et al.,[6] Livnat et al.,[7] Leppert et al.,[8] Kerner,[9] Mannino et al.,[10] Averback and Wiglesworth,[11] Anderson,[12] Hainline and Nagey,[13] and Enbom (present report).

insertion of the umbilical cord. Ironically, velamentous insertion is found more frequently in the live-born twin rather than the stillborn twin. Benirschke[3] found velamentous insertion of the umbilical cord in 14 of 60 diamniotic-monochorionic twins and in eight of 63 diamniotic-dichorionic placentas. Livnat et al.[7] reported three cases of velamentous insertion, with one involving the surviving twin and two involving the stillborn twin, again emphasizing the frequency of this cord anomaly.

Vascular anastomosis between placentas is noted frequently with monochorionic placentas. In an extensive evaluation of 200 twin placentas by Benirschke, 11 of 63 (17.5%) identical twins demonstrated evidence of twin transfusion. Sekiya and Hafez[17] reported evidence of fetal transfusion syndrome in seven of 44 (16%) monochorionic placentas, and Tan et al.[18] found the same process in 35 of 482 (7.5%) random twins studied. The severe form of the twin-to-twin transfusion syndrome may also potentially produce fetal death.

In Benirschke's large study of twin placentas, a more unique process was demonstrated. A twin gestation with intrapartum death of one twin was delivered at 32 weeks with a monochorionic-monoamniotic placenta and velamentous insertion of one cord. The live-born twin had apneic spells and respiratory distress, as well as muscular rigidity. This neonate died on the second day of life, and autopsy revealed bilateral renal cortical necrosis, numerous vessels occluded by thrombi, splenic infarcts, and cortical brain stem fibrin deposits. The author proposed thromboplastin-rich blood transfused to the live-born twin via the placental anastomosis as a pathogenesis.[3] Regardless of the mechanism of death, the common placental vascularity allows persistent flow to the detriment of the surviving twin.

Table VI. Total live-born twins with major morbidity or death

	No.	*Percentage*
Alive and well	21	53.8
Major morbidity or death	18	46.2

Data from Melnick,[2] Benirschke,[3] Durkin et al.,[4] Yoshioka et al.,[5] Moore et al.,[6] Livnat et al.,[7] Leppert et al.,[8] Kerner,[9] Mannino et al.,[10] Averback and Wiglesworth,[11] Anderson,[12] Hainline and Nagey,[13] and Enbom (present report).

Moore et al.[6] reported three twin pregnancies with antepartum death of one twin. Neonatal death occurred with two of the live-born twins, and the third live-born twin survived. The two neonatal autopsies revealed renal and central nervous system lesions consistent with the findings of Benirschke. The one surviving twin had a unilaterally calcified, nonfunctioning kidney. Yoshioka et al.[5] also reported three infants with cerebral palsy and angiographic evidence of multicystic encephalomalacia thought to be due to arteriolar occlusive disease secondary to embolic phenomenon from the deceased twin. These studies provided direct autopsy evidence and radiographic evidence of a vascular etiology.

Durkin et al.,[4] in a review of 281 mentally retarded children, reported a disproportionately high number of twins. Within the twin group were eight cases involving antepartum death of one twin and subsequent delivery of a severely retarded and spastic twin sibling. These authors also proposed an etiology of intrauterine disseminated intravascular coagulation.

Pritchard and Ratnoff[19] reported alterations in the maternal clotting mechanism with retention of a dead fetus. This occurred with greater frequency if the pregnancy continued more than 5 weeks after the death. Interestingly, this did not occur in the reviewed cases involving antenatal death of one twin, even though the fetus was retained far longer than 5 weeks on many occasions. Maternal coagulopathy has been reported by Skelly et al.[20] involving a triplet pregnancy with antenatal death of two of the three fetuses. One died in the second trimester, and the other in the third trimester. Maternal disseminated intravascular coagulation was noted and treated initially with heparin and subsequent delivery, but the remaining live-born infant showed no evidence of the coagulopathy.

Mannino et al.[10] proposed a vascular etiology for a rare congenital skin defect that caused a slough of the skin in the region of the scalp, trunk, and thighs. A degenerative rather than an atrophic process was suggested because of the early death in the third or fourth month of gestation. Ischemia and skin slough that resulted from a circulating thromboplastic phenomenon from the deceased twin was thought to be responsible.

Other abnormalities of delivery, such as dystocia produced by a fetus papyraceus, delayed passage of a fetus papyraceus and placental tissue, as well as postpartum infections, have occurred.[8, 9]

As with other twins, the incidence of prematurity with the live-born twins is high and a significant concern. Both Cases 1 and 2 were premature, as were the reported gestational lengths of 45.2% of the reviewed cases (see Table IV).

Survival of the live-born twin was noted in 82.1% (Table V) of the cases evaluated. However, if the incidences of death and major morbidity are combined, 46.2% (Table VI) had an unfavorable outcome. These figures are most likely high and misleading because of the fact that most series were gathered with a specific complication to report and did not include the most likely circumstance, i.e., a favorable outcome for the surviving twin that goes unreported. The series reported by Melnick[2] from the National Collaborative study is a more inclusive group.

None of the cases studied in the antepartum period demonstrated evidence of a fetal coagulopathy. Concern over antepartum testing, dysmaturity, malpresentation, and maternal disease was noted, but no skin, renal, vascular or central nervous sytem defects could be predicted before newborn evaluation. This suggests an intrinsic pattern of circulation between the twins that, in turn, triggers a disseminated intravascular coagulation process but fails to trigger a disseminated intravascular coagulation process in the mother. Hyalinization and/or fibrosis eventually occurs after death and may limit and eventually stop the shared circulation before abruptio placentaes or a more widespread process occurs to affect the maternal clotting mechanism. Possibly the remaining twin's circulatory pattern prevents subsequent degeneration or production of a thromboplastic material in the extraovular circulation.

In recent articles by Hainline and Nagey[13] and Hanna and Hill,[14] high-risk management for this specific problem was outlined. Maternal rest, nutrition, hematinics, and careful observation for hypertensive disease, dysmaturity, and prematurity are important, as with all twins.

With a greater likelihood of prematurity, dysmaturity, abnormal presentation, and placental vascular anomalies, a high-risk protocol and obstetric center are advised for evaluation and delivery. Early diagnosis of twins, as well as early recognition of the fetal death, is important in subsequent management.

The presence of a double amnion is helpful, but should not lead one to be complacent. Most monozygotic twins have separate amniotic cavities and still have vascular anastomoses. A single cavity presents a situation of very high risk that requires consideration for delivery as soon as maturity is reached, if all other factors are stable.

Serial measurement of fetal growth, assessment of amniotic fluid volume, and placental grading are done every 3 to 4 weeks until the last month and then may be done more frequently as part of the fetal evaluation. Weekly or biweekly fetal movement testing and serum estriols are recommended.

Serial evaluation of the maternal clotting mechanism, including fibrinogen, prothrombin time, partial thromboplastic time, platelet counts, and evaluation for fibrin degradation products, is recommended. Even though antepartum diagnosis of disseminated intravascular coagulation involving only the surviving twin has not been made, maternal disseminated intravascular coagulation has been detected, especially if preeclampsia is present.

Delivery is predicated on multiple factors and should be considered if abnormal fetal testing, the presence of toxemia, a maternal coagulation deficit, or other high-risk conditions coexist.

As pointed out by Melnick[2] and reemphasized by Hanna and Hill,[14] early delivery has not prevented the serious brain damage or the renal and cutaneous complications of intrauterine disseminated intravascular coagulation. This by itself does not appear to be a reason for premature delivery.

Our personal experience appears to be the same as that of Hanna and Hill, however. Once the diagnosis of intrauterine death of one twin is verified, the pressure on the medical care team, the patient, and the patient's family is tremendous. This situation is made worse by the fact that predicting all major fetal complications is not possible by antepartum testing or an apparently uncomplicated delivery.

Because of the possible pathologic condition of multiple organs of the live-born fetus, the pediatric staff plays a significant role in recognizing signs and symptoms of central nervous system, renal, circulatory, and cutaneous defects caused by a disseminated intravascular coagulation process. The pediatrician should be alerted to the anticipated problems well before delivery in order to provide for early, appropriate hematologic studies as soon as possible after delivery. Placental evaluation is also helpful in order to determine zygosity and the presence of placental vascular anastomosis. As with Yoshioka et al.[5] and Moore et al.,[6] specific radiographic procedures to evaluate the central nervous system and renal system may be indicated. Newborn follow-up is then needed to assess progressive growth and development. The family should make people aware of the unique antepartum event involving the stillborn sibling.

I wish to thank Ronald G. Marcum, M.D., for his assistance.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Basil W. Maloney, La Mesa, California. When I read that this subject was to be presented, my interest was sparked since we had several such cases at our hospital. Grossmont is a 400 bed suburban community hospital. Since January 1, 1980, when records were first kept on multiple births with fetal death, until May 1, 1984, there were 11,407 deliveries, of which 11,308 were singleton births with 77 stillbirths. There were 99 multiple births, of which 4 had antenatal death of one or more fetuses. The details of the cases are given in Table I.

Dr. Enbom presented a report of two cases of twins with fetal death of one fetus. He then surveyed the literature on the subject and summarized it well. He found extensive material focusing on the placenta in an attempt to explain and predict the course of these cases. As physicians, we have a tendency to overlook the placenta. This report, along with the review of articles by Dr. Kurt Benirschke, refocuses our attention on the placenta.

The condition of intrauterine fetal death of one twin is rare enough that not all obstetricians will be the principal in even one case. Therefore, each patient is managed in a highly individual manner.

In the sonogram, we have a very valuable tool for diagnosing and monitoring the course of pregnancy. In the cases presented and in those reported in the literature, the sonogram was the sheet anchor of evaluation. Recently, we all received an extensive report on the indications for the use of sonograms in our speciality. The more the sonogram is used, the more are the indications found.

Among the cases presented in the literature, which were at tertiary teaching services, very extensive parameters were established for monitoring the cases, as well there should be, to help determine the course of the cases and to be used for teaching purposes.

The technology, physicians, nurses, and technicians are rapidly being transferred to the community hospitals where most obstetric care is rendered.

I have two questions for Dr. Enbom. (1) Do you foresee routine sonograms being obtained in all pregnancies, and if so, at what point? (2) In this day of cost-effective medical care, what are the minimum essential elements of quality care of this type of case?

Dr. Lyman Rust, Hanford, California. Recently, we saw a 34-year-old woman who had an uneventful pregnancy, labor, and delivery. After the placenta was delivered, I, as is my custom, reached into the uterus to ascertain that all the placenta and membranes had been removed, and there I found a little, macerated fetus. My question is, If we do not perform routine ultrasonography, how are we going to diagnose these cases? If we do not perform ultrasonography on everyone, and we probably should not, we will miss this type of problem from time to time.

Dr. Frederick Hanson, Davis, California. I will carry Dr. Rust's comments even a step further. We performed an amniocentesis on a woman with twins. One was a dead fetus with brown fluid, and chromosomes grew out trisomy 8. When she was delivered at term there was absolutely no evidence of a twin being present. So it could disappear.

Table I. Summary of cases

Patient	*Age (yr)*	*Parity*	*First visit*	*Sonograms*	*Fibrinogen*	*Labor and delivery*	*Placenta*
R. V. V.	22	Gravida 3, para 2	18 wk	18 Wk—twins, one viable 24 Wk—decrease in size of dead fetus		Spontaneous vaginal Twin A—fetus papyraceus Twin B—male 7 pounds 10 ounces Normal, term	
D. B.	24	Gravida 3, para 1, abortus 1; History of cesarean section for breech 4-pound female infant; postpartum death	26 wk	32 Wk—twins, normal 38 Wk—no heart beats		Trial induction—repeat cesarean section, stillborn twins	Cords from dividing membranes, dichorionic diamniotic fused
J. B.	25	Gravida 2, para 0, abortus 1	7-8 wk	23 Wk—triplets, 1 viable, 2 nonviable	Low 165 mg/dl At delivery—440 mg/dl	Elective cesarean section	Trichorionic triplets
C. S.	28	Gravida 3, para 2	6 wk	6 Wk—two gestational sacs, one with fetal heart motion 8 Wk—repeat, one viable fetus	All normal	28 Wk, bleeding Spontaneous delivery, neonatal death on same day Abortus passed	

DR. JOHN MAY, San Diego, California. As Dr. de Castro said, we frequently go back to our practice and find something that is apropos from discussions like this. My case was that of a patient in whom twins were diagnosed at 15 weeks. At about 27 weeks, she developed severe polyhydramnios, and a second sonogram was obtained. The smaller twin had developed hydrops, but both twins were living. Early labor and early effacement of the cervix then occurred, and delivery ensued. The smaller twin who had died one day previously was delivered first and was anencephalic. The second twin survived even though delivery was at 27 weeks' gestation.

DR. GEORGE WINCH, San Francisco, California. We too had one case similar to these. Our patient was a 32-year-old primi gravid woman in whom a twin pregnancy was diagnosed at 12 weeks by ultrasound. A subsequent ultrasound examination was performed at about 23 or 24 weeks, at which time no second twin was seen. This patient did well until about 32 or 33 weeks, when she developed a mild polyhydramnios. An amniocentesis was performed at about 35 weeks, with no appreciable abnormalities noted in the fluid. Labor occurred at 36 weeks. During labor, the fetal monitor showed very severe bradycardia, and a cesarean section was performed. The infant was a mildly hydropic single fetus with no evidence of a twin. The infant was in a hematologic crisis. Initially, disseminated intravascular coagulation was diagnosed. Every conceivable abnormality was searched for. This infant had multiple hospitalizations and then died within about 6 months. To this day, the etiology of the hematologic episode has not been determined. Fortunately, the mother was studied completely at the University of California. No hematologic abnormalities were noted. She later became pregnant and was delivered of a normal infant.

DR. ENBOM (Closing). Dr. Maloney, I appreciate your review and comments and presentation of these rare, isolated cases. No one has a large series and this points out the need for a larger registry. Sonography has made a very great difference in this particular diagnosis. The largest series of cases reported was in 1948, by James Kindred, Ph.D (AM J OBSTET GYNECOL 1944;48:642, who reported 150 cases, but they were described in terms of the pathologic features and fibrosis of the placenta and the pathologic condition of the fetus. Nothing was reported in regard to the actual intrauterine environment. Everything changed significantly at the time sonography was introduced. Unfortunately, the rarity of this particular entity makes routine sonography difficult to justify. Once a diagnosis is made, one could justify sonography on almost everyone.

Dr. Rust, I appreciate your comments about routine ultrasound. In regard to Dr. Hanson's comment, we also had a case, that I did not report, diagnosed as twins at 14 to 16 weeks on ultrasound examination. At the time of delivery, we could find no evidence of placental fibrosis or components of a second fetus.

Amniotic fluid embolism: An overview and case report

Jay I. Mulder, M.D.
Covina, California

This article gives an overview of amniotic fluid embolism, which still carries a fatality rate of approximately 86% and which accounts for 9% of all maternal deaths. A case report is presented which ended with a fatal outcome. Photomicrographs show fetal squames and lanugo hairs in the pulmonary capillaries as well as ones aspirated from the right atrium. The treatment is discussed in terms of acute primary and acute secondary care. Acute primary care centers around the prompt recognition and treatment of pulmonary edema. This is apparently due to the mechanical blockade of the pulmonary vasculature and particulate matter from the amniotic fluid and also to an anaphylactoid reaction adding to the pulmonary arteriolar spasm. The acute secondary treatment deals with combating the almost inevitable disseminated intravascular coagulation and uterine atony. Being always alert to the possible occurrence of this condition and being able to institute appropriate therapy rapidly are necessary for a successful outcome. (AM J OBSTET GYNECOL 1985;152:430-5.)

Key words: Amniotic fluid embolism, treatment

The first substantive article on this subject appeared in *JAMA* in 1941. Two researchers from the University of Chicago, Paul Steiner and C. C. Lushbaugh, described a rare but very lethal entity that they correctly labeled maternal pulmonary embolism by amniotic fluid. Their observations were so astute that little has been added over the years to our current knowledge.

The original article cited an incidence of one in 8000 deliveries between the years of 1930 and 1940.[1]

In a report from England the incidence was said to be one in 80,000 deliveries.[2]

In our own country it has been noted that as deaths from hemorrhage, infections, and toxemia have decreased, amniotic fluid embolism has increased in relative importance as a cause of maternal deaths, with a reported case fatality rate of 86%. In the period 1968 to 1975, 454 women were reported to have died from amniotic fluid embolism, representing 9% of all maternal deaths. The percentage is greater than that from placenta previa, sepsis, and eclampsia. The study committee on maternal mortality has documented mortality rates for amniotic fluid embolism of 2.7 to 29.8 deaths per 100,000 live births.[3]

Although amniotic fluid embolism has traditionally been associated with term delivery, amniotic fluid embolism has recently been found to be an important cause of abortion-related deaths as well.

Since 1972 amniotic fluid embolism has accounted for 12% of all deaths related to legally induced abortion in the United States.[3] However, this still is only 0.2 deaths per 100,000 legal abortions.

The risk of death during induced abortion increased with advancing gestational age, presumably reflecting a dose response to either larger volumes of amniotic fluid or more particulate matter suspended in the amniotic fluid, or both.

At 12 weeks' gestation the mean volume of amniotic fluid is 50 ml. This volume increases to approximately 400 ml by midpregnancy. These data suggest that when volume is <50 ml, the risk of death is negligible.[3]

Incidence of amniotic fluid embolism has also been reported in cases of saline-induced abortions as well as therapeutic amniocentesis in the treatment of polyhydramnios.

Case presentation

The patient was a 44-year-old Mexican woman, gravida 8, para 6, with last pregnancy 10 years earlier. Her labors had varied from 4 to 16 hours, and the largest baby weighed 9 pounds. There was a noncontributory past history. In the present pregnancy there was a normal prenatal course. The estimated gestational age was 44 weeks.

The patient went into spontaneous labor and was admitted to the hospital shortly thereafter at 6:00 PM. Contractions were somewhat irregular, the membranes were intact, cephalic presentation was at the −3 station, dilatation was 2 cm with 80% effacement. The fetal heart rate was 140 bpm and regular. By 10:15 PM the contractions had become stronger and more regular. The cervix was 3 to 4 cm dilated, and the head was at the −1 station. The membranes were artificially ruptured. A moderate amount of meconium-stained fluid was obtained. The fetal heart rate was regular at 140 bpm. The contractions remained regular and were 3

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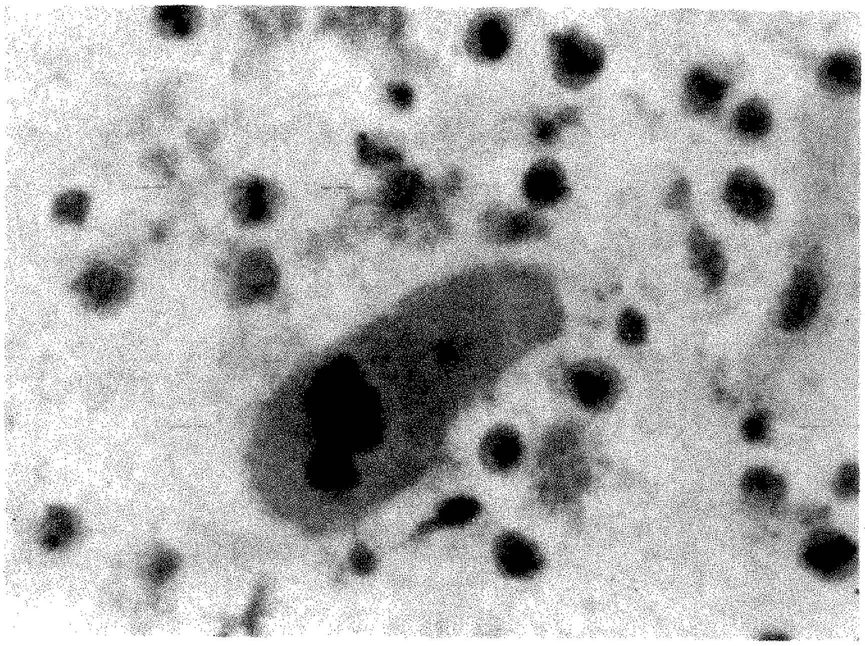

Fig. 1. Aspirate from the right atrium showing a cell compatible with a syncytiotrophoblast. (×280.)

to 5 minutes apart, lasting 30 to 40 seconds; however progress was slow. The patient had received no medication for pain or to stimulate uterine contractions.

At 1:15 AM an irregularity in the fetal heart rate was noted, followed by slowing to 60 bpm. The patient was given oxygen, with no appreciable change in the fetal heart rate, so preparations were made for cesarean section. At this time she suddenly experienced pain in the uterus. It was steady, continual pain, although the uterus was not tender to the touch and there was no evidence of tetanic contractions. There was no vaginal bleeding. Shortly thereafter the patient became very agitated, anxious, and dyspneic. Within minutes there was evidence of peripheral vascular collapse. The blood pressure and pulse were not obtainable. She was intubated and an immediate cesarean section was performed.

An extremely depressed term male infant was delivered but subsequently died.

There was no evidence of abruptio placentae or disseminated intravascular coagulation. There was no response to cardiopulmonary resuscitation, and the patient was pronounced dead at 3:00 AM. The total time from the first symptom to death was <2 hours. A diagnosis of amniotic fluid embolus was made.

The postmortem examination showed the cardiovascular system to be essentially normal; the heart weighed 360 gm with no evidence of chamber dilatation of hypertrophy.

The respiratory system showed evidence of pulmonary edema. The right and left lungs weighed 740 and 680 gm respectively, with cut surfaces exuding large amounts of frothy, pink fluid.

The genital system showed the cervix as well as both the ectocervix and the endocervix to be edematous and hemorrhagic. The uterus showed no evidence of hemorrhage into the myometrium.

Findings for the remainder of the postmortem examination were negative.

Microscopic examination

Several smears were made from the buffy coat of blood from the right atrium. Multiple cells were seen which were compatible with trophoblastic origin (Fig. 1). In addition, nucleated squames were present. The permanent sections of the lung showed abundant fetal squames within terminal branches of pulmonary arteries (Fig. 2).

In the lung there were also eosinophilic proteinaceous material within alveoli as well as numerous macrophages. The most prominent finding was abundant fetal-type squames within smaller branches of the pulmonary arteries. Focally these squame cells plug the arterial lumina.

Notably absent was mucin. Perhaps if special stains such as Attwood's stain had been available, these fetal elements would have been seen.

Predisposing factors

The following six predisposing factors were identified:

1. The average age of the patient with amniotic fluid embolism is greater than a group similar in size and selected at random. The average age is 32.

2. Occurrence of amniotic fluid embolism is more common (8:1) among multiparous women.

3. The uterine contractions are stronger than the

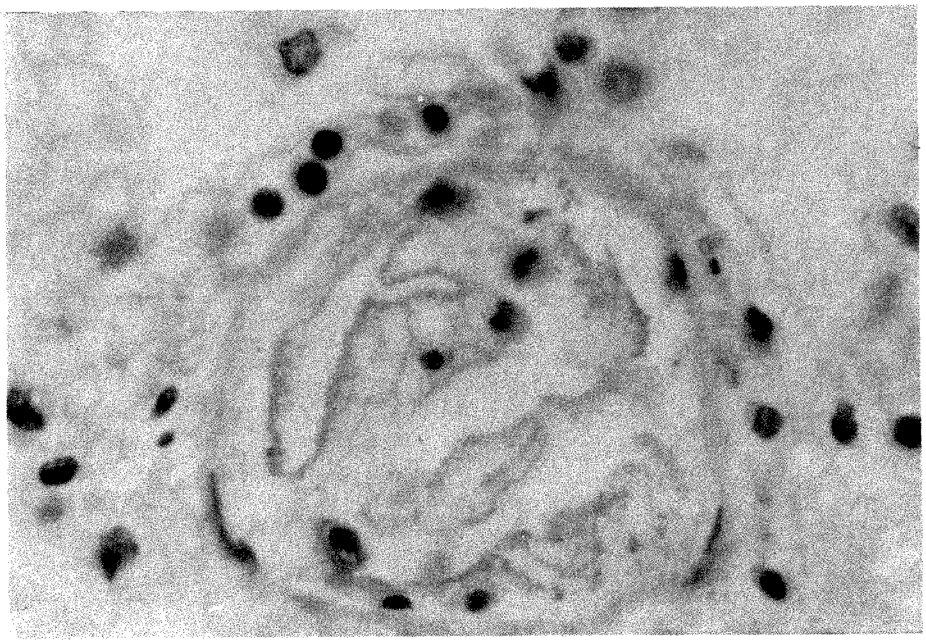

Fig. 2. Pulmonary capillary filled with nucleated squames. (×280.)

average. Occasionally they are described as tetanic and frequently as very hard. It was postulated that the contractions prepared a route for the entrance of the emboli into the maternal sinuses by (1) loosening or tearing the membranes or placenta and then (2) forcing the emboli into the venous channels.

4. The amount of particulate matter is significant, being most particularly mucin from meconium, secondarily squamous cells, and to a lesser degree, vernix.

5. The majority of fetuses studied in the original article were larger than average. There was also a disproportionately large number of still births. It is felt that presence of a dead fetus reduced the strength of the membranes as well as greatly increased the amount of particulate matter in the amniotic fluid.[1]

6. In one series 45% of cases of amniotic fluid embolism were associated with premature placental separation.[4] In fact, many writers believe this to be in one form or another the main route of entry; others include placenta previa, uterine rupture, or involvement of the placental site in a cesarean section incision.[5]

Cardinal signs

The condition is often heralded with a chill, shivering, sweating, anxiety, coughing, vomiting, and convulsions. Chest pain is rarely present. Pulmonary edema with ensuing pink, frothy sputum occurs quickly. If the patient survives the shocklike episode, bleeding secondary to disseminated intravascular coagulation and uterine atony almost invariably occur.[5]

If the patient survives the initial pulmonary insult, the incidence of disseminated intravascular coagulation is said to be close to 100%. This is apparently due to the coagulant activity of amniotic fluid. It has been suggested by Courtney[5] that amniotic fluid itself may cause hypotonia of the uterus as well.

Occasionally there may be a delayed onset of the syndrome as long as several hours after the delivery, notably by cesarean section. This might be explained by amniotic fluid becoming trapped in the uterine veins immediately after delivery and then being gradually released into the maternal circulation with the diminution of the uterine tone.[5]

Treatment

Treatment must necessarily be thought of in terms of acute primary and acute secondary care.

Acute primary care concerns evaluation and treatment of the cardiopulmonary systems. When signs of pulmonary edema are present, and it invariably is, it must be treated vigorously. This is apparently due to a mechanical blockade of the pulmonary vasculature with particulate matter from the amniotic fluid and also to an anaphylactoid reaction adding to the pulmonary arteriolar spasm.[5]

Pulmonary edema. Pulmonary edema should be treated as follow: (1) Institute positive pressure oxygen therapy, probably via an endotracheal tube. (2) Administer hydrocortisone, 2 to 4 gm intravenously. (3) Attempt to alter bronchospasm and arteriolar spasm with terbutaline sulfate (Brethine), isoproterenol (Isuprel), or aminophylline. (4) Institute general acute supportive measures such as use of semi-Fowler position, administration of morphine sulfate, and digitalization with a rapidly acting agent. (5) If possible, establish an avenue to measure pulmonary and central venous pressure, preferably with a pulmonary artery balloon flotation catheter.[6,7]

Hemorrhage. The acute secondary treatment deals with combating the almost inevitable hemorrhage secondary to disseminated intravascular coagulation and uterine atony.

The treatment of hemorrhage secondary to disseminated intravascular coagulation consists of cryoprecipitate, 4 to 6 units, and fresh-frozen plasma.

If a favorable response is not adequate, a bolus of heparin, 2500 to 5000 U, may be used. This dosage is thought to be as effective as a larger dose and less apt to produce additional hemorrhage.

Intravenous oxytocic agents are used to control uterine atony. Prostaglandin $F_{2\alpha}$ should be used if the usual oxytocic agents are ineffective.

Comment

In their original article Steiner and Lushbaugh[1] stated in their summary that they hoped the diagnosis of amniotic fluid embolism could be made during the life of the patient. Forty-three years later we are still unable to adequately diagnose this condition before death. However, recent work by Duff[6] at Letterman Hospital in San Francisco suggests that sometimes a diagnosis can be made during life.

The principle technique for establishing the diagnosis remains aspiration of blood from the central circulation via a central venous pressure catheter or pulmonary artery balloon flotation catheter. Direct smears of the blood may thus be prepared with special stains.

Hemodynamic measurements obtained by right heart catheterization studies may also help confirm the diagnosis. Characteristic findings of the acute embolic event include elevations in pulmonary capillary wedge pressure, main pulmonary artery pressure, and central venous pressure; decreased systemic blood pressure; decreased cardiac output.

When an acute amniotic fluid embolism occurs, the maternal electrocardiogram may show acute right heart strain. On x-ray examination the main pulmonary vessels are found to be engorged, and there are interstitial, intra-alveolar, and bilateral infiltrates. A radionuclide lung scan may confirm the presence of ventilation perfusion defects but cannot differentiate between venous and amniotic fluid embolism. Arterial blood gases typically show hypoxemia, hypercapnea, and a mixed respiratory-metabolic acidosis when disease is severe.[6]

For a successful outcome it is necessary that one always be alert to the possible occurrence of this condition and be able to institute appropriate therapy rapidly.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. John E. Mayo, San Diego, California. Amniotic embolism is a problem we will encounter rarely in our practices, but if we do, it will be a memorable and frightening experience. Dr. Mulder very accurately summarizes the incidence, predisposing factors, mortality rates, signs, symptoms, and treatment of this spectacular obstetric complication. He also presents a case that ended with the usual fatal outcome. There is little to add or criticize in his review, but a few additional comments may be of value.

From a treatment point of view, the concept of an acute primary phase and an acute secondary phase makes a great deal of sense. The cardiac and pulmonary systems are integrally related in the presentation of signs and symptoms and are likewise essentially related in considering treatment. The onset of hemorrhagic signs is usually a later occurrence but not necessarily so. As Morgan[1] points out in his review of 272 cases in 1979, the presenting symptoms are respiratory, 51%; cardiovascular, 27%; convulsive, 10%; hemorrhagic, 12%.

From a conceptual point of view, therefore, it may be useful to look at the mechanisms thought to be involved in the development of this syndrome in a slightly different way. Table I shows the chronology of events may actually be visualized as more of a three-phased process with the first two being closely related and overlapping. The respiratory phase is initiated by the particulate matter in amniotic fluid and subsequent anaphylactic reaction causing bronchospasm, mechanical vascular obstruction, and some vasospasm. The appro-

Table I. Chronology of events

Phase	*Initiating agent*	*Signs and symptoms*	*Diagnosis monitoring*	*Treatment*
Respiratory	Particulate matter Anaphylactoid reaction	Anoxia Tachypnea Cyanosis Convulsions Coma	Respiratory rate Blood gases Blood smear for amniotic fluid embolism V-Q scan	Oxygen Positive end-expiratory pressure Corticosteroids Isuprel Aminophylline Brethine
Cardiovascular	Vasoactive substance	Shock Increase in pulmonary blood pressure Right heart strain	Electrocardiogram Central venous pressure catheterization Swan-Ganz catheter	Digitalization Tourniquets
		Decrease in systemic blood pressure	Blood pressure monitoring	Vasopressors Fluids
Hemorrhagic	Coagulation activator (activator of factor X?)	Bleeding Disseminated intravascular coagulation	Clot examination Coagulation studies	Heparin Blood products
		Uterine atony	Uterine tonus	Oxytocic agents Uterine massage Aortic compression

Table II. Use of routine Attwood's staining technique to determine the presence or absence of squamous cells*

	Study subjects							
	Before delivery		*Immediately after delivery*		*1 hr after delivery*		*2 hr after delivery*	
Stains	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Positive	10	91	16	100	14	100	13	100
Negative	1	9	0	0	0	0	0	0
Total	11		16		14		13	

*DiMarzo SV, Saltzstein S, Key T, Resnik R. Unpublished data, 1984.

priate treatment of this phase is the early and aggressive use of positive end-expiratory pressure, oxygen, hydrocortisone, and bronchodilators. The cardiovascular phase is secondary to the first but markedly enhanced by a nonparticulate substance present in amniotic fluid which causes marked pulmonary hypertension and its sequelae. The additional modalities of treatment are outlined in Table I. The hemorrhagic phase is also initiated by a nonparticulate coagulation factor and perhaps an atonic uterine factor that completes the syndrome complex. The treatment of this phase involves the *early* prophylactic use of heparin (which is somewhat controversial), blood products, and oxytocic agents. The use of prostaglandin $F_{2\alpha}$ in the treatment of uterine atony may also be controversial, since Kitzmiller and Lucas[2] postulated in 1972 after animal studies that it may indeed be prostaglandin $F_{2\alpha}$ that is the vasoactive substance responsible for some of the cardiovascular effects seen with this syndrome. The 15-methylated form mentioned in this review, however, may not be harmful.

The accurate diagnosis of amniotic fluid embolism without a fatal outcome is very difficult. Because of an unusually high incidence of positive Atwood stains for squamous cells in blood taken from right heart samples in patients with obstetric complications at the University of California (San Diego) School of Medicine, and since it is known that amniotic fluid rarely enters the pulmonary circulation,[3] Dr. Stephen DiMarzo, then a resident but now in practice at Scripps Clinic in La Jolla, undertook to evaluate the Atwood staining method as used at University of California (San Diego). (DiMarzo SV, Saltzstein S, Key T, Resnik R. Presence of squamous cells in central venous blood during pregnancy: a diagnosis of amniotic fluid embolism. Unpublished observations, 1984.) He used right heart samples from any obstetric patient requiring a central venous pressure or Swan-Ganz catheter. He also studied four nonpregnant control subjects. Table II shows that with the usual technique, virtually 100% of pregnant patients had positive stains before, during, and after delivery. All of the control samples were positive. The technique was changed by meticulously cleaning the slides, wearing bonnet and gloves to collect and stain the samples, filtering all stains, and replacing them in fresh jars. As can be seen in Table III, the modified technique mark-

Table III. Use of "modified" Attwood's staining technique to determine the presence or absence of squamous cells*

	Study subjects							
	Before delivery		*Immediately after delivery*		*1 hr after delivery*		*2 hr after delivery*	
Stains	*n*	%	*n*	%	*n*	%	*n*	%
Positive	0	0	1†	20	0	0	2‡	40
Negative	4	100	4	80	5	100	3	60
Total	4		5		5		5	

*DiMarzo SV, Saltzstein S, Key T, Resnik R. Unpublished data, 1984.

†Few isolated squamous cells along edge of slide.

‡Obvious contaminating "floater"; two isolated squamous cells.

edly improved the specificity of the test. All the nonpregnant control samples were negative. This information emphasizes the importance of scrupulously evaluating laboratory techniques before attributing clinical significance to results.

I would like to congratulate Dr. Mulder on a thorough and very clinically helpful review of the subject.

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Dr. E. Forrest Boyd, Los Angeles, California. I would like to go back about 24 years to illustrate a time variance of which we should all be aware.

The patient was a 35-year-old woman, gravida 4, para 2, whose other infants weighed 9 lb. and 8½ lb. In this case at 39 weeks' gestation, she delivered an 8 lb 11½ oz female infant. Labor was spontaneous and hard and lasted about 5 hours. The membranes ruptured spontaneously at approximately 1½ hours before delivery. Continuous catheter caudal analgesia was administered for 2 hours prior to the spontaneous delivery over a midline episiotomy. An old cervical laceration was denuded and repaired. The uterus was mildly relaxed but responded to massage and oxytocics. At 1½ hours after delivery the patient was in bed, having talked to the family, and was asleep. Twenty minutes later, or 1 hour 50 minutes after delivery, she was found in shock with disseminated intravascular coagulation. The frantic therapeutic cascade was futile in spite of blood, hysterectomy, and so forth. Autopsy by John Budd revealed three V-shaped lacerations exposing the venous sinuses, extending up from the old repaired laceration. Lanugo hair and fetal squamous cells were found in a right ovarian vein thrombosis, as well as in the heart, lungs, and brain. The lesson to remember from this case is to beware of the masking effect of analgesia, which could delay the diagnosis.

Dr. Charles Kimball, Seattle, Washington. My recollection of Paul Steiner's material regarding amniotic fluid embolism fatalities is that the presence of fetal squames and lanugo hairs in the basal brain arterioles produces ischemia and hypoxia in the hypothalamic-hypophyseal circulation. Hypoxia in this vital area of the visceral nervous system is known to induce hypotensive shock and vascular collapse. Evidence from recent research strongly suggests shock from any and perhaps all causes related to overwhelming release of enkephalin and other opioid peptides in central nervous system and circulating fluids, which compounds the central nervous system anoxia and may be the lethal mechanism in amniotic fluid embolism fatalities.

The opiate antagonist (Narcan) has been found to reverse shock and vascular collapse in both animal and clinical studies. I think it should be used in all hypotensive shock, since it has no known adverse effects even in a very large dosage.

Dr. Charles Stipp, Seattle, Washington. Eleven years ago I presented to this society, during a show-and-tell presentation, the use of an intra-aortic balloon catheter for the control of uterine hemorrhage associated with amniotic fluid embolus. Use of intra-aortic balloon catheter is a modality that should be remembered. It buys time and allows catching up on blood replacement so that definitive care can be accomplished. Incidentally, this patient survived.

Dr. Mulder (Closing). I think Dr. Kimball touched on the important point, as did Dr. Boyd, that embolism that occurs late is often due to amniotic fluid trapped in the maternal sinuses, which is released later. This is most often noted following a cesarean section. I think this explains the delayed amniotic fluid embolism that we occasionally see.

Analysis of 2136 genetic amniocenteses: Experience of a single physician

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Between 1979 and 1984, 2136 midtrimester genetic amniocenteses were performed by a single physician at the University of California (Davis) Medical Center. The medical records were reviewed for maternal age, amniocentesis indication, ultrasound findings, location of placenta, location of the needle insertion (transplacental versus nontransplacental), color of the amniotic fluid, results of prenatal testing, complications of procedure, and pregnancy outcome. Follow-up data were available for 88% of the pregnancies. There were 38 miscarriages (1.9%), 18 stillbirths (0.9%), and four neonatal deaths (0.2%), resulting in a total postprocedural loss rate of 3.1%. Miscarriage within 2 weeks of amniocentesis occurred in only 0.4% of procedures (seven of 1918). No significant difference in pregnancy outcome was noted between transplacental and nontransplacental amniocentesis. Greenish brown discolored amniotic fluid was found in 3.6% of procedures (76 of 2136). In this group there was a 14.5% fetal loss rate with an overall 22.4% adverse outcome. (AM J OBSTET GYNECOL 1985;152:436-43.)

Key words: Genetic amniocentesis, transplacental, miscarriage, discolored amniotic fluid, stillbirths

Amniocentesis was first described in 1882 as a method for treating polyhydramnios. Barr's classic publication in 1949 opened the way for Fuchs and Riis's work on antenatal sex determination. Steel and Bregs's successful culture of amniotic cells and the work of many others ultimately led to the use of amniocentesis for prenatal diagnosis of chromosomal disorders, neural tube defects, and inborn errors of metabolism.

This report was stimulated by the publication of Porreco et al.[1] in which it was stated that anterior placentation was associated with a twofold increase in pregnancy loss compared with posterior placentation. Most published studies on the hazards of midtrimester prenatal diagnosis represent multiinstitutional and multiinvestigator reports.[1-15] The prenatal diagnosis program at the University of California (Davis) Medical Center at Sacramento offers the unique opportunity to review the risks of midtrimester amniocentesis in a large patient population without the variables associated with multiple physicians and institutions. The experience of a single physician will be reviewed.

Methods

The University of California (Davis) Medical Center prenatal diagnosis program, part of a statewide network of 19 centers, has performed more than 3000 midtrimester amniocentesis procedures since 1976. This report concerns over 2000 amniocenteses performed by one of the authors (F. W. H.) between 1979 and 1983.

The authors believed that to evaluate properly the procedure-related morbidity and loss and the risks of transplacental amniocentesis on morbidity and mortality, all cases with preamniocentesis complications, such as bleeding and cramping, or with potential increased risk factors, such as multiple gestation, elevated α-fetoprotein, or chromosomal abnormalities revealed at amniocentesis, should not be considered. These cases would a priori be at high risk for subsequent adverse outcome. There were 218 of these a priori high-risk cases and 1918 remaining a priori low-risk cases. Data for each variable were not available for all subjects studied. The data were evaluated for the effect of maternal age (over and under 35 years), gestational age at the time of amniocentesis (weeks since last menstrual period ± 1 week), location of amniocentesis (transplacental or not), and color of the amniotic fluid. To compare our data with those in other published studies, pregnancy loss data were divided into the following categories: 2 weeks after amniocentesis, <28 weeks' gestation (miscarriage), ≥28 weeks' gestation (stillbirth), and neonatal death (within 1 week of birth).

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Table I. Indications for amniocentesis in 2136 patients undergoing midtrimester prenatal diagnosis

Indication	*Frequency*	*%*
Maternal age	1651	77.3
Prior trisomy 21 child	70	3.3
Family history of Down's syndrome	25	1.2
Prior trisomy 13 child	4	0.2
Prior trisomy 18 child	13	0.6
Prior XO chromosome anomaly	6	0.3
Prior XXY chromosome anomaly	1	0.0
Child with other defect	5	0.2
Balanced translocation	4	0.2
Prior neural tube defect	79	3.7
Family history of neural tube defect	34	1.6
Prior omphalocele	4	0.2
Prior hydrocephalus	10	0.5
Fetal abnormality	2	0.1
Metabolic disease	12	0.6
Family history of X-linked disorder	11	0.5
Anxiety	199	9.3
Other	6	0.3
Total	2136	100.0

Table II. Gestational age (weeks since last menstrual period) at the time of amniocentesis based on biparietal diameter measurements

Gestational age (wk)*	*Frequency*	*%*
13	10	0.5
14	50	2.3
15	213	10.0
16	621	29.1
17	687	32.2
18	344	16.1
19	115	5.4
20	50	2.3
21	22	1.0
22	14	0.7
23	1	0.0
24	4	0.2
25	4	0.2
26	1	0.0
Total	2136	100.0

*Weeks since last menstrual period ± 1 week.

The program at the Sacramento Medical Center is comprehensive. All patients are screened and individually counseled by a geneticist. Real-time and static B-mode ultrasound are used to study fetal viability and gestational age, to determine placenta location, to identify fetal and pelvic abnormalities, and to select the site for amniocentesis. Amniocentesis is then performed. After application of a povidone iodine (Betadine*) skin preparation, a 1% lidocaine (Xylocaine†) local anesthetic is administered, and a 20-gauge spinal needle is used for amniocentesis. For chromosomal analysis and α-fetoprotein assay, 24 to 36 ml of amniotic fluid is removed. Rh immunoglobulin (300 μg) is routinely administered to Rh-negative patients, unless the father of the baby is documented to be Rh negative. Anterior placentation is not considered a contraindication to amniocentesis. Attempts are made to locate a placenta-free site; if one is not available, a site at the margin of the placenta away from the umbilical cord insertion is sought.

Statistical analysis. The data were keypunched, verified, and entered into a file on a University of California VAX 11/780 computer. Frequency tables were generated by the statistical analysis system. Statistical significance of two-way tables was assessed by χ^2 analysis. The effect of a transplacental tap on the probability of miscarriage or neonatal death, adjusted for mother's age, weeks of gestation, and color of amniotic fluid, was evaluated by multiple logistic regression.

Results

The demographic data of the study population were not significantly different from other published studies.[1-15] Initially 2136 subjects were evaluated. Subject ages varied from 16 to 49 years, and 1521 subjects were >35 years of age.

The indications for amniocentesis are given in Table I. The most common indication was maternal age (77.3%); maternal anxiety was second (9.3%).

Table II shows that most amniocenteses were performed between a gestational age of 15 and 19 weeks since the last menstrual period.

Anterior placental implantation was found in 46.9% (1001) of patients and posterior in 42.0% (898); the remainder, 11.1%, were considered to be other (fundal, lateral) or not stated.

Amniocentesis, however, was carried out through placental tissue in only 28.7% (613) of cases and through nonplacental tissue in 71.3% (1523).

The frequency of needle insertion and the necessity for a repeat tap are given in Table III; 96% of first-attempt amniocenteses were successful, with 2% requiring a second visit. The majority of repeat taps were performed because adequate fluid could not be obtained at the initial amniocentesis.

Table IV indicates the color of the fluid obtained at

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*The Purdue Frederick Company, 50 Washington St., Norwalk, Connecticut.

†Astra Pharmaceutical Products, Inc., 7 Neponset St., Worcester, Massachusetts.

Table III. Frequency of needle insertion and indications for repeat tap

Attempts	*Frequency*	%
One insertion	1887	88.3
Two insertions	148	6.9
Three or more insertions	10	0.4
Repeat tap, no fluid	37	1.7
Repeat tap, no growth	5	0.2
Not stated	49	2.2
Total	2136	100.0

Table IV. Color of amniotic fluid obtained at amniocentesis in 2136 patients

Color	*Frequency*	%
Straw	1843	86.3
Red, clearing	140	6.6
Red throughout	21	1.0
Greenish brown	76	3.6
Not stated	56	2.6
Total	2136	100.0

Table V. Pregnancy outcome in 2136 patients undergoing midtrimester genetic amniocentesis

Outcome	*Frequency*	%
Normal male infant	894	45.9
Normal female infant	917	47.0
Miscarriage at 28 weeks	38	1.9
Stillbirth at 28 weeks	18	0.9
Neonatal death at 7 days	4	0.2
Abnormal infant (not detectable prenatally)	34	1.7
Premature birth at 35 weeks	27	1.4
Small-for-gestational age infant	17	0.9
Unknown	187	8.8
Total	2136	100.0

amniocentesis. Straw-colored or initially red but clearing fluids were considered normal and made up 92.9% of the fluids obtained; 4.6% of fluids were considered abnormal (red throughout or greenish brown). When all 2136 subjects were considered, 14.5% of abnormal fluids were found to be associated with a fetal or neonatal death.

Table V shows that 92.9% of the deliveries were considered to be normal term deliveries and that 3% of fetal outcomes resulted in some type of loss (miscarriage prior to 28 weeks, stillbirth from 28 weeks to term, or neonatal death). Table VI demonstrates the relationship of maternal age and outcome in the low-risk group. The observed rates of adverse outcomes were higher in women ≥35 years, but did not reach statistical significance.

Table VII shows the potential effect on complications of traversing the placenta during amniocentesis. There was no increased adverse effect associated with transplacental amniocentesis. Only seven miscarriages (0.4%) occurred within 2 weeks of amniocentesis.

Table VIII shows the relationship of the location of the tap to later pregnancy outcomes. There are fewer observed abnormal outcomes (6.5%) in the transplacental group than in the nontransplacental group (7.4%), but the difference is not statistically significant.

Table IX shows the cases divided by color of amniotic fluid and by subsequent pregnancy outcomes. The high rate (13.5%) of miscarriage, stillbirth, and neonatal death in patients with greenish brown fluid is striking, as is the high rate of premature/small-for-gestational age infants (5.8%). Pregnancies with straw-colored fluid were generally at lowest risk. The associations are highly significant ($p < 0.001$).

Table X shows that there was a slight but statistically significant ($p < 0.05$) trend for poorer outcomes with earlier gestational age at the time of amniocentesis.

Logistic regression analysis related the occurrence of miscarriage, stillbirth, or neonatal death to gestational age, maternal age, and color of fluid and to whether the tap was transplacental or not. Each risk factor was adjusted for the others. Only the color of the fluid was statistically significant in this analysis ($p < 0.05$).

Comment

Numerous studies both at the large-scale national collaborative level as well as the multiinstitution and single institution level have addressed themselves to the risks and safety of amniocentesis for midtrimester prenatal diagnosis.[1-15] Amniocentesis-related miscarriage rates have varied from a low of 0.3% to 0.7% as reported by Philip and Bang[10] to a high of 2.89% reported in the National Institute of Child Health and Human Development collaborative study.[2] Unfortunately, it is difficult to compare studies since a uniformity of definition is lacking. Most studies designated loss prior to 28 weeks as a miscarriage and beyond 28 weeks as a stillbirth. Other studies have only described total losses.

O'Brien[13] recently reviewed nine major published studies reporting on fetal risks of amniocentesis. He reported an approximately 1% mean rate of vaginal bleeding (1.2%) and fluid leakage (1.0%). Comparable figures for our prenatal diagnosis program are 0.4% and 0.2%, respectively. In 9586 patients a mean abortion rate of 1.6% (range, 1.0% to 2.9%) was observed. A prospective investigation of spontaneous abortion following amniocentesis revealed a 0.6% increased abortion rate in subjects as compared to controls (2.1%

Table VI. Pregnancy outcome by maternal age in 1918 low-risk pregnancies undergoing midtrimester genetic amniocentesis*

	Age (yr)			
	Under 35		*35 and older*	
Outcome	*No.*	*%*	*No.*	*%*
Normal	470	94.4	1161	92.4
Miscarriage and neonatal death	11	2.2	38	3.0
Abnormal infant (not detectable prenatally)	8	1.6	25	2.0
Premature/small–for–gestational age infant	9	1.8	31	2.4
Total	498	100.0	1255	100.0

*A priori low-risk singleton pregnancy. Information was missing for 165 pregnancies.

Table VII. Complications of midtrimester genetic amniocentesis by location of amniocentesis in 1918 patients*

	Location			
	Not transplacental		*Transplacental*	
Complication	*No.*	*%*	*No.*	*%*
None	1215	98.6	507	98.8
Cramping	2	0.2	1	0.2
Bleeding	3	0.3	3	0.6
Fluid leakage	4	0.3	0	0.0
Pain	1	0.1	0	0.0
Miscarriage (within 14 days)	5	0.5	2	0.2
Fetal injury	1	0.1	0	0.0
Other	1	0.1	0	0.0
Total	1232	100.0	513	100.0

*A priori low-risk singleton pregnancy. Information was missing for 173 pregnancies.

Table VIII. Pregnancy outcome compared to location of amniocentesis in 1918 patients undergoing genetic amniocentesis*

	Location			
	Not transplacental		*Transplacental*	
Outcome	*No.*	*%*	*No.*	*%*
Normal	1448	92.7	483	93.6
Miscarriage (under 28 weeks)	22	1.8	8	1.6
Stillbirth	13	1.1	3	0.6
Neonatal death	2	0.2	1	0.2
Abnormal infant (not detectable prenatally)	24	2.0	9	1.7
Premature birth at <35 wk	16	1.3	8	1.6
Small–for–gestational age infant	12	1.0	4	0.8
Total	1237	100.0	516	100.0

*A priori low-risk singleton pregnancy. Information was missing for 165 pregnancies.

versus 1.5%). The spontaneous miscarriage rate (<28 weeks) after exclusion of a priori high-risk cases in our study was 1.7%. If, however, one considers a spontaneous abortion as being procedure related only if it occurs within 2 weeks after the procedure or if it follows postamniocentesis bleeding or leakage of fluid, the rate was 0.4%. Total fetal loss and neonatal death in our study amounted to 3.1% compared to the 4.1% reported by O'Brien[13] from three studies. The United States and Canadian collaborative studies[24] were unable to demonstrate an increased risk of prematurity, pregnancy loss, or fetal morbidity. O'Brien[13] in his report concluded that there was a real fetal and neonatal risk associated with second-trimester amniocentesis, the magnitude of which remains controversial.

The study of Porreco et al.[1] reported a twofold in-

Table IX. Pregnancy outcome in 1918 patients compared to color of amniotic fluid obtained at genetic amniocentesis*

	Color							
	Straw		*Red, clearing*		*Red throughout*		*Greenish-brown*	
Outcome	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Normal	1425	93.7	107	91.5	19	95.0	41	78.8
Miscarriage, stillbirth, and neonatal death	34	2.2	6	5.1	1	5.0	7	13.5
Abnormal infant (not detectable prenatally)	26	1.7	4	3.4	0	0.0	1	1.9
Premature/small–for–gestational age infant	36	2.4	0	0.0	0	0.0	3	5.8
Total	1521	100.0	117	100.0	20	100.0	52	100.0

*A priori low-risk singleton pregnancy. Information was missing for 208 pregnancies.

Table X. Pregnancy outcome compared to gestational age at the time of genetic amniocentesis in 1918 low-risk pregnancies*

	Weeks of gestation					
	13-16		*17-18*		*19-26*	
Outcome	*No.*	*%*	*No.*	*%*	*No.*	*%*
Normal infant	680	92.2	787	93.1	164	95.3
Miscarriage, stillbirth, and neonatal death	24	4.3	22	2.6	3	1.7
Abnormal infant (not detectable prenatally)	15	2.0	16	1.9	2	1.2
Premature/small–for–gestational age infant	18	2.4	19	2.2	3	1.7
Total	737	100.0	844	100.0	172	100.0

*A priori low-risk singleton pregnancy. Information was missing for 165 pregnancies.

creased fetal loss associated with anterior placentation. Though it was not stated as such, it was assumed that transplacental amniocentesis was the suspect risk factor in those cases. In our study we were unable to demonstrate any difference in complications or pregnancy outcome with transplacental amniocentesis.

Maternal age was not a statistically significant factor affecting outcome in this selected population. There is a trend for procedures done at $\leq$16 weeks of gestation to have outcomes slightly poorer than those done later in pregnancy. In part this may reflect the greater opportunity to undergo spontaneous abortion. Samuels[16] has stressed the need for use of the fetal life table method for predicting fetal loss rates.

The color of the amniotic fluid was the only variable that proved statistically significant with regard to adverse outcome. This finding has been reported by others,[2, 6, 7] but the degree of risk was unexpected. Twenty-two percent of the greenish-brown fluids had a less than optimal pregnancy outcome and will be the subject of a future report.

Relatively few published reports address the influence of physician experience with regard to risks of amniocentesis. Young et al.[12] could show no difference, whereas Verjaal et al.[15] showed a higher rate of fetal loss associated with less physician experience. The frequency of bloody taps has been reported to decrease with experience.[2, 4] The Canadian collaborative study[4] was able to demonstrate no difference in success at obtaining fluid and physician experience.

In summary, the data reported in this study are controlled for physician experience and therefore may represent the minimal figures for the risks and complications associated with midtrimester prenatal genetic amniocentesis under the optimal circumstances of an experienced operator with a stable support system of counseling, ultrasound, and laboratory analysis.

We were unable to confirm the previously reported increased fetal loss associated with anterior placentation.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. THOMAS G. MOYERS, San Diego, California. Above and beyond Dr. Hanson's effort to analyze the many facets of risk associated with midtrimester genetic amniocentesis, his unique personal experience, which is presented here, deserves recognition as the most extensive ever reported by an individual physician. This volume of experience alone, when added to previously reported data, makes a significant contribution to our understanding of the risks of genetic amniocentesis.

The author makes no specific claim as to the role of physician experience in reducing risk. He does suggest a lower abortion rate in his cases compared with a combined study review. Yet his data when evaluated for overall pregnancy loss are comparable to several reports of individual or even multiple physician experience. In addition, the exclusion of the so-called a priori high-risk cases, defined as those with a history of bleeding or cramping, multiple gestation, elevated α-fetoprotein or chromosomal abnormality, as well as the lack of data for some variables, varying from table to table, makes the interpretation of the remaining data somewhat difficult. There is a suggestion that the 218 a priori high-risk cases excluded from analysis in Tables VI through X have a pregnancy loss rate higher than the remaining cases. As stated by the author, 14.5% of all abnormal fluids were associated with pregnancy loss, while in the selected cases it would appear that 11.1% of such abnormal fluids (eight of 72) were associated with pregnancy loss. Was the pregnancy loss rate higher for multiple pregnancies? Further information regarding these excluded cases would be helpful.

Several authors previously reporting their experience with amniocentesis or reviewing previous studies have emphasized the importance of similarity in study design to enable meaningful comparison of published reports. Dr. Hanson has made a real effort to accomplish this, as stated in his paper, but there remains a real need for overall standardization so that meaningful accurate comparisons can be made. In this regard and relating to the study presented here, Dr. Hanson has chosen to classify fetal losses at up to 28 weeks' gestation as miscarriages, but would it not be more appropriate to use some standard relating to potential neonatal survival, such as 24 or 26 weeks' gestation, particularly in this day of effective treatment of the tiny premature infant? It should be noted that the ratio of 18 stillbirths (over 28 weeks) to four neonatal deaths, reported here, seems somewhat unusual. In my experience babies are more frequently born alive even at gestational ages of <28 weeks.

In correlating gestational age at the time of amniocentesis with pregnancy loss in Table X, it is observed that earlier attempts are related to increased loss. Since genetic amniocentesis is recommended by most to be performed from 15 to 18 weeks, this comparison might well be more meaningful if the categories presented were as follows: <15 weeks, 15 to 18 weeks, and >18 weeks.

Another question relates to the category abnormal (not detected prenatally) which includes a significant number of cases in several of the outcome tables presented. No definition of this category appears in the text of the report; it needs clarification.

One frequent observation by previous investigators has been an association between multiple taps or attempts and increased pregnancy loss. Although data are presented regarding number of attempts, the author makes no comparison of this factor with outcome.

My own observation, confirmed by others, is that late sequelae to genetic amniocentesis may be significant. Such consequences may be reflected by premature labor, premature rupture of membranes, intrauterine growth retardation, or late pregnancy hemorrhage. The review by O'Brien, included as reference 13, reports associations with increased cesarean delivery rates and with orthopedic deformations of the lower extremities which may be attributed to prolonged oligohydramnios. Has Dr. Hanson made any observations related to these associations?

This report represents a significant contribution to our knowledge of the consequences of genetic amniocentesis. Despite the present enthusiasm of some and the wide publicity relating to chorion villus sampling, my personal feeling is that genetic amniocentesis will continue to play a significant role in prenatal genetic diagnosis. The present study confirms our impression that the procedure has minimal yet definable risks.

Dr. Robert Goodlin, Omaha, Nebraska. I would argue that the expertise in doing amniocentesis concerns the ultrasonographer. In our clinic there are at least two technicians who are superexperts in locating amniotic fluid. When any of our staff works with these two women, we never miss in obtaining amniotic fluid. Under different circumstances, however, the fluids are often bloody and sometimes we fail.

One problem which we see repeatedly in the older, multigravid individual is the frequent Braxton-Hicks contractions. Many times we can locate the amniotic space, only to have it disappear during a prolonged contraction. When we measure the amniotic fluid pressure during these Braxton-Hicks contractions, it is often increased. I have been puzzled as to why these apparent contractions at 16 weeks do nothing to the cervix. The women usually state that they can feel them, however. My question is, "What does Dr. Hanson do when confronted with frequent Braxton-Hicks contractions and an amniotic space that is shifting?"

My third question concerns the indication for amniocentesis when the patient has had a previous fetus with hydrocephalus. Dr. Hanson had a category for "other anomalies," and I would presume that would include hydrocephalus, since we know that the subsequent pregnancies can be associated with other neural tube anomalies. However, I am unaware of any specific indications for amniocentesis for hydrocephalus.

Dr. S. Gainer Pillsbury, Long Beach, California. I would like to ask Dr. Hanson a question. Since there seems to be an increased incidence of pregnancy loss, is the finding of greenish or brownish fluid an indication for fetal surveillance at the time of fetal viability with nonstress or contraction stress tests and that sort of thing starting at 26 or 28 weeks?

Dr. Frank Gamberdella, Santa Barbara, California. Dr. Frigoletto reported, I believe in *Obstetrics and Gynecology* about 6 or 8 months ago, the need for simultaneous ultrasound-directed needle aspiration as opposed to scanning and then subsequently inserting the needle. I was wondering whether in your studies this was done on a routine basis or only on occasion.

Along the lines of what Dr. Goodlin stated, there are radiologists in this country who are doing amniocentesis. I can tell you that in Santa Barbara one of our radiologists, who is an ultrasonographer, has probably done the majority of second-trimester genetic taps, the reason being that he is an excellent ultrasonographer. Would you comment on that approach.

Dr. Richard Allen, Portland, Oregon. I have two questions. Is the brownish or bloody fluid incidence increased by the fact that you are making transplacental taps about 28% of the time? Do you think transcervical chorionic villi sampling will make amniocentesis obsolete?

Dr. Hanson (Closing). No, I do not think amniocentesis will become obsolete for a variety of reasons—you already knew I was going to say that. One is that with chorionic villus biopsy you lose all of your ultrasound benefits for picking up structural abnormalities. We frequently have patients coming in for one indication yet we find something totally unanticipated. We are averaging about 40 or 50 dead fetuses a year prior to a tap.

I have not simultaneously scanned and tapped any individual, partly because I perform 18 or 20 taps consecutively. Other problems are with sterilization and with the need for about five hands to operate the equipment. I have said from the podium many times I am only as good as the ultrasound technician. The three women I worked with were superb. They were better than the radiologists who are doing ultrasound studies. We have the same political problems in our town and within our hospital as you have experienced in Santa Barbara, but I do not want to get into that. Regarding hydrocephalus, it is well known that hydrocephalus can occur one time and a neural tube defect in another area in a subsequent pregnancy, and that is the reason some of these patients are being scanned. We have never failed to obtain an amniotic fluid specimen from any patient. I do not do anything about contractions. If a contraction happens to be in the way, we have the patient walk while we check another patient, and it usually disappears. You see contractions in almost all patients. As far as multiple gestations are concerned, I am planning to write a paper on that. I have experience with 55 sets of twins and one set of quadruplets. We have not lost a single fetus that has not been severely structurally abnormal or had abnormal chromosomes. We have been able to successfully tap every sac. Fortunately, the quadruplets were only in two sacs, containing three fetuses and one fetus, which made it a little easier. We used dye in all multiple gestations.

We set out to prove two points. One was to look at the risks of transplacental amniocentesis and to gain more than hearsay data. I think we accomplished that. We also wanted to attempt to look at the true risks of amniocentesis, at the impact of combined versus single institution studies, and at the variable experience in those situations that are known to have higher risks of spontaneous abortions. I hope we accomplished those goals. We could easily discuss only cases that have complete data. My biostatistician informed me that 10% incomplete data was insignificant. There was no reason, because of the large numbers and the time over which we did this study, to suspect there would be any peculiar trend other than what we have been seeing over the years. My personal experience is approximately 4000 cases now. I do not think I could improve my technique. I think the greatest difficulty is in those situations in which you know you should not tap and you go ahead and do it anyway. I am forced sometimes into that situation because of the unusual distances some of our patients have to travel.

It is difficult to scrutinize one's own work and discuss it in such forums without seeming defensive and/or egotistical—I guess I will do both. Our data are larger than the United States or Canadian collaborative studies. I certainly think that the miscarriage rates of 0.4% within 2 weeks or 1.7% up to 28 weeks or total loss of 3% are very favorable and as good as any published study of which I am aware. Thank you for the opportunity to present these data.

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Abdominal pregnancy: A study of twenty-one consecutive cases

Jack G. Hallatt, M.D., and James A. Grove, M.D.
Los Angeles, California

Early abdominal pregnancy is self-limited by hemorrhage from trophoblastic invasion, with complete abortion of the gestational sac that leaves a discrete crater which is sometimes difficult to identify. Advanced abdominal pregnancy survives the hemorrhage of trophoblastic invasion and partial tubal abortion and implants secondarily in the first trimester on any adjacent structure. It may progress to term if not diagnosed or interrupted by abruptio placentae and have spurious labor and fetal death. A case of cornual abortion with secondary implantation on the uterus is discussed. (AM J OBSTET GYNECOL 1985;152:444-9.)

Key words: Abdominal pregnancy, hemoperitoneum, cornual abortion

Ninety-nine percent of all pregnancies are intrauterine. One percent is extrauterine. Ninety-eight percent of all extrauterine pregnancies are intratubal, 1% is ovarian, and 1% is primary or secondary peritoneal implantations. The etiology of extrauterine pregnancy is primarily entrapment of the zygote or gamete in fibrotic pockets in the endosalpinx which are due to prior infection or surgical adhesions or occlusion. This etiology does not apply to primary abdominal pregnancy or ovarian pregnancy. Early abdominal pregnancy is a primary peritoneal implantation which usually aborts early in the first trimester because of hemorrhage which disrupts the implantation site. Advanced abdominal pregnancy occurs when the first-trimester implantation is partially disrupted and the viable pregnancy continues active implantation through the twelfth gestational week, involving secondarily all adjacent structures. After the twelfth week, the placenta grows in thickness and circumference only, and secondary implantation and hemorrhage from trophoblastic invasion no longer occur.[1] The pregnancy may progress to term unless diagnosed or interrupted by the many accidents to which it is subject. A review of the literature by Nesbitt,[2] in 1955, revealed 258 cases of lithopedion, which is the end result of undiagnosed and untreated advanced abdominal pregnancy. The present study is further evidence of the difficulty in diagnosing unruptured ectopic pregnancy, which is the only way to prevent the catastrophic morbidity of advanced abdominal pregnancy. A study of these curious natural experiments in human reproduction adds to our incomplete knowledge of the mechanisms of human reproduction. A much needed classification of abdominal pregnancy is suggested.

Material and analysis

This study of abdominal pregnancy is part of a detailed analysis of 1475 patients with ectopic pregnancies admitted to Kaiser Permanente Hospital, in Los Angeles, from 1953 to 1984. Table I shows the obstetric experience and classifies abdominal pregnancies into three groups. Ovarian pregnancy is the most common abdominal pregnancy, composing 1% of all ectopic pregnancies. It is a distinctly separate clinical entity that occurs exclusively in the ovary, which has no peritoneal covering. Its features have been previously reported,[3] and it is excluded from this study. The peritoneal implantations fall into two separate groups, based on the duration of the pregnancy. Table II summarizes the findings in early abdominal pregnancy, which cannot be distinguished from tubal pregnancy preoperatively. The first symptom was vaginal bleeding, which occurred in six of the 12 patients. The second symptom which led to the diagnosis was the sudden severe pain of hemoperitoneum, which averaged 767 ml and was diagnosed by culdocentesis. Operation occurred early in the first trimester, 52 days from the first day of the last normal menstrual period, or an average of 38 gestational days. In Case 6, who was infertile, hemorrhage occurred on gestation day 16 by dates and basal body temperature. At operation, the tubes and ovaries were normal and a small clot was noted on the anterior surface of the uterus. When the clot was removed, it left a small, discrete bleeding crater which was resected and

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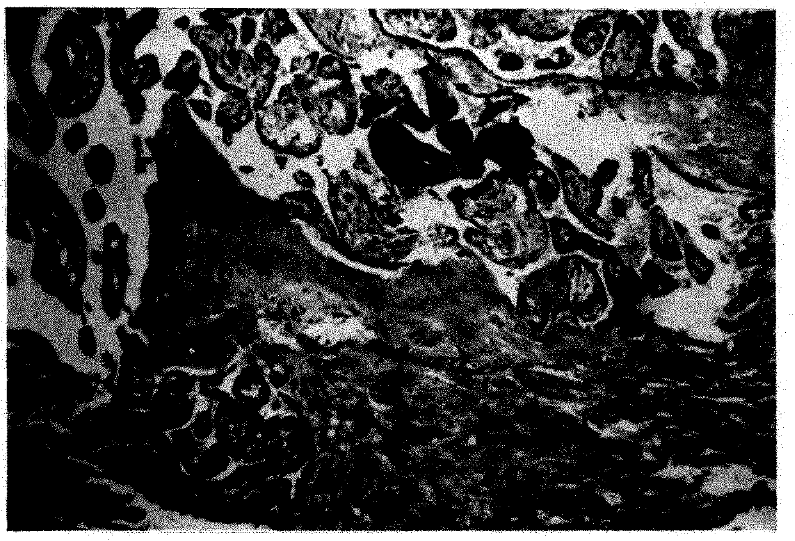

Fig. 1. Placental invasion of myometrium at exit of cornual fistula.

Table I. Ectopic pregnancy, obstetric experience from 1953 to 1984 at Kaiser Permanente Hospital, Los Angeles

Total No. of deliveries	120,000
Ectopic pregnancies	1475
Tubal pregnancies	1439
Abdominal pregnancies	36
Ovarian pregnancies	15
Early abdominal pregnancies	12
Advanced abdominal pregnancies	9

revealed villi microscopically. The gestational sac was not identified. A crater was described in six of the 12 cases. In Cases 3 and 4, the crater was on the tube and not in it, as demonstrated by tubal patency with methylene blue dye injected into the fundus with the cervix occluded. There was no tubal enlargement or hematosalpinx. In most cases the management consisted of suture hemostasis. Cases 10, 11, and 12 present an interesting clinical entity. In spite of a significant hemoperitoneum, the implantation site could not be identified. The tubes and ovaries were normal. A small gestational sac was floating in the hemoperitoneum in case 12. In cases 10 and 11, the general surgeon explored the upper abdomen. A normal-appearing corpus luteum was seen in all three cases. The postoperative course was normal. The characteristic feature of early abdominal pregnancy is a complete abortion of the gestational sac that leaves a discrete crater.

Table III summarizes the features of nine advanced abdominal pregnancies. The patients, who averaged over 33 years of age, were older than the usual patients with ectopic pregnancies. Two patients gave a history of a prior ectopic pregnancy. Five patients gave a history of pain and/or bleeding in the first trimester, which was regarded as a threatened abortion. In Case 3 the patient had a right tubal pregnancy 1 year after an abdominal pregnancy. The abdominal pregnancy required removal of the left fallopian tube. Four patients had massive hemoperitoneum from abruptio placentae which required an emergency operation that led to the diagnosis. Four normal-appearing fetuses were stillborn, and one stillborn fetus had severe pressure deformities. Three normal-appearing fetuses were living

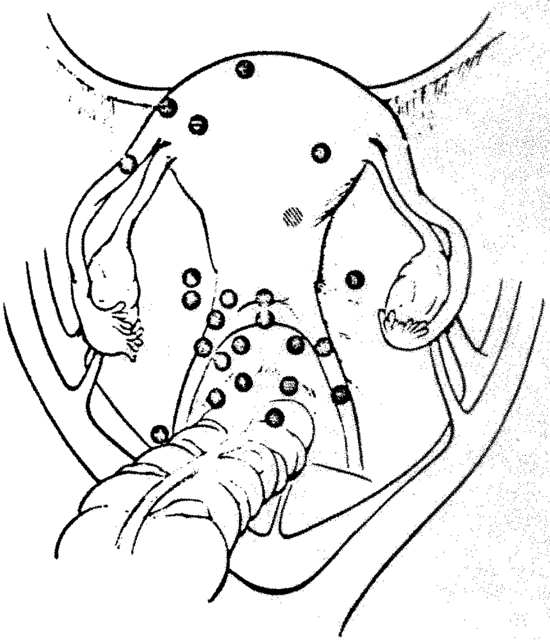

Fig. 2. Sites of previously reported primary pelvic peritoneal pregnancies. (From Obstet Gynecol 1968;31:649-53. Reproduced by permission of the American College of Obstetricians and Gynecologists.)

Table II. Early abdominal pregnancy: summary of significant findings in 12 patients

Case No.	*Year*	*Age (yr)*	*Race*	*Parity*	*Days from last normal menstrual period to*			*Hemoperitoneum (ml)*
					Bleeding	*Pain*	*Operation*	
1	1954	23	White	0	42	41	72	100
2	1962	42	White	5	47	60	82	2000
3	1972	30	Black	0	0	45	45	650
4	1974	23	Black	1	0	45	45	1000
5	1975	33	Black	1	27	48	54	2000
6	1980	37	White	1	0	31	31	350
7	1981	34	Black	2	0	36	38	250
8	1981	28	White	2	0	60	60	600
9	1982	31	Black	4	0	44	47	650
10	1974	21	White	1	32	62	65	500
11	1975	26	White	0	28	33	34	1000
12	1977	28	White	2	28	35	49	100
Average		29.66 yr					51.6 days	767

Table III. Advanced abdominal pregnancy: summary of significant findings in nine patients

Patient	*Year*	*Age (yr)*	*Race*	*Parity*	*Days from last normal menstrual period to*			*Hemoperitoneum (ml)*	*Transfused (units)*
					Bleeding	*Pain*	*Operation*		
1 E. C.	1954	37	White	0	34	34	203	0	0
2 O. Y.	1960	35	White	1	159	159	164	500	0
3 M. F.	1966	31	Black	1	52	0	127	0	0
4 L. M.	1967	36	White	2	50	56	287	0	4
5 A. M.	1970	27	White	1	35	35	180	1700	3
6 L. M.	1972	32	Black	1	24	0	280	0	0
7 A. G.	1974	39	White	1	74	94	174	0	3
8 D. B.	1976	25	Black	1	0	210	252	2500	4
9 E. M.	1984	36	White	0	96	98	100	4000	4
Average		33.1 yr					196 days	1008	

but previable. It was necessary to remove the placenta in four cases for hemostasis. The implantation was in the pelvis in all nine cases. The fallopian tube was intimately involved in eight of the nine cases. The possible exception was in Case 8, which was thought to be a cornual abortion with secondary implantation. The tube was removed in seven of the cases in which the placenta was removed. In Case 1 the patient had a diagnosis made by hysterography and was delivered of a healthy viable baby (2 pounds, 15 ounces) with a harelip and cleft palate. Since the implantation involved the sigmoid colon, the placenta was left in situ. The patient had an uneventful postoperative course and 2 years later was delivered vaginally of a term infant without incident. In Cases 6 and 8, the implantation involved the uterus and a hysterectomy was required for hemostasis. In Case 4 spurious labor at 41 weeks' gestation was followed by fetal death. The baby was grossly normal when delivered abdominally. The implantation was in the cul-de-sac in Case 6 and involved the sigmoid colon. Hemostasis was very difficult. The patient had a stormy postoperative course for 1 month and improved after drainage of a pelvic abscess. In Case 8 the patient had a right salpingectomy, in 1974, for ectopic pregnancy. No uterine defect was noted at that time. Two years later at the time of operation for a 36-week abdominal pregnancy implanted on the right broad ligament and uterus, a 1 to 2 cm defect was noted in the right cornu. The fistula was adjacent to the gestational sac and placenta. Fig. 1 is a microscopic section of the placenta invading the uterus adjacent to the fistula. No endometrium or endosalpinx could be iden-

Transfused (units)	*Implantation*	*Embryo*	*Surgical procedure*	*Comment*
0	Right broad ligament	Aborted	Wedge resection of ovary	Vaginal delivery at term, 1956
4	Cul-de-sac	7 cm crown-rump length	Hemostasis	Left hydrosalpinx
0	Left tube	Aborted	Hemostasis	Tube and ovary normal
2	Right cornu	Aborted	Hemostasis	Tube and ovary normal
4	Cul-de-sac	Aborted	Right salpingo-oophorectomy	Postoperative hematoma
0	Uterus	Aborted	Resection	16 days' gestational age
0	Sigmoid colon	Aborted	Left tube	Tubal cautery, 1976
1	Right cornu	Aborted	Resection of right cornu	Intrauterine contraceptive device, 3 yr
0	Cul-de-sac	Aborted	Resection	Intrauterine contraceptive device, 2 yr
0	Unknown	Not found	Abdominal exploration	Tube and ovary normal
2	Unknown	Not found	Abdominal exploration Intrauterine contraceptive device, 2 yr	Tube and ovary normal
0	Unknown in abdomen	Floating	Abdominal exploration Intrauterine contraceptive device, 3 yr	Tube and ovary normal

Implantation	*Fetus*	*Surgical procedure*	*Comment*
Pelvis	Live, 2 pounds 15 ounces	Placenta not removed	Vaginal delivery at term, 1956; fibroids on hysterosalpingogram, 1956
Right pelvis	Previable	Right salpingo-oophorectomy + placenta	Fibroids
Left pelvis	Previable	Left salpingo-oophorectomy + placenta	Ectopic, 1967
Left pelvis	Stillborn	Left salpingo-oophorectomy + placenta	Spurious labor
Right cornu	Stillborn	Right salpingo-oophorectomy + placenta	Amniotic sac intact
Left pelvis	Stillborn	Left salpingo-oophorectomy + placenta, hysterectomy	Fimbria, hysterosalpingogram
Left pelvis	Previable	Placenta removed, left salpingo-oophorectomy + placenta	Pelvic abscess
Right pelvis	Stillborn	Hysterectomy, left salpingo-oophorectomy placenta	Right cornual fistula 2 cm
Cul-de-sac	Stillborn	Placenta removed, hysterectomy	Fibroids

tified in the fistula to indicate its origin in this pregnancy. A history of pain and bleeding in the first trimester could not be elicited.

Comment

At the time of ovulation the mature ovum is covered by a sticky cumulus of granulosa cells which must be lysed before fertilization can occur. The ovum may remain adherent to the follicle, become fertilized, and implant in the ovary as an ovarian pregnancy. It may float freely in the peritoneal cavity, become fertilized, and migrate to the opposite tube and implant as a tubal pregnancy. Transmigration and contralateral implantation occur in 20% of all ectopic pregnancies.[4] The ovum may be fertilized and gravitate into the cul-de-sac or any location in the peritoneal cavity, and on about day 6 will implant on whatever structure it is adjacent to as an abdominal pregnancy. This documents that fertilization can and does occur in the peritoneal cavity, and that implantation can and does occur without endometrium. The role of the endometrium is primarily to prevent trophoblastic invasion of maternal blood vessels and hemorrhage. This hemorrhage is the pathologic course of early ectopic pregnancy.

Ninety-nine percent of the zygotes which result in pregnancy reach the endometrial cavity and implant as a blastocyst. At this time, human chorionic gonadotropin is produced and by its luteotropic action stimulates decidua formation and the succulent hypersecretory endometrium known as Arias-Stella phenomenon, which by an unknown mechanism protects the maternal blood vessels and myometrium from trophoblastic invasion. Trophoblastic invasion and implantation cannot occur in decidua. This protects the uterine cavity from complete obliteration. There is no Arias-Stella reaction or adequate decidua in the ovary, tube, or peritoneal cavity to prevent the maternal hemorrhage which disrupts the implantation site and aborts the gestational sac as early as the sixteenth gestational day, as documented by Case 6 in the early abdominal pregnancy series. This leaves a bleeding crater which is the characteristic feature of primary peritoneal implantation. Pregnancies have been reported in every part of the peritoneal cavity, including the liver, spleen, and omentum. Friedrich,[5] in 1968, reported a case of primary peritoneal pregnancy implanted on the anterior leaf of the broad ligament which aborted and left a crater that contained villi. He found 23 additional cases in the literature, the locations of which are shown in Fig. 2. Apparently, the peritoneum does not allow the blastocyst to become completely imbedded, as occurs in the uterine endometrium and endosalpinx. Therefore, the hemorrhage occurs in the confined implantation site and aborts the gestational sac early. The endosalpinx is a more favorable implantation site than the peritoneum, and the hemorrhage may not completely disrupt the pregnancy. Trophoblastic invasion and secondary implantation of viable villi can continue through the twelfth week after a partial tubal abortion or intraligamentary extension.[1] This is thought to be the mechanism of most advanced abdominal pregnancies, since the tube was intimately involved in eight of the nine cases. Five of the patients gave a history of vaginal bleeding and/or pain in the first trimester, which is consistent with rupture or partial abortion. Secondary implantation of a completely aborted gestational sac (which is a common event in ectopic pregnancy) has never been proved. Secondary implantation apparently requires maintenance of maternal circulation for viability and aggressive trophoblastic invasion of adjacent structures. Case 7 was probably a case of secondary implantation which advanced to 36 weeks before diagnosis. Cornual pregnancy after salpingectomy has been reported.[6, 7] The contracting uterus can gradually abort the viable cornual pregnancy and prevent significant bleeding. This is the only apparent explanation for the large hole in the right cornu of the uterus immediately adjacent to the placental implantation on the anterior surface of the uterus and bladder. The right cornual fistula which admitted a finger did not contain membranes or placenta, but villi do invade the peritoneal exit of the fistula. This is consistent with partial progressive cornual abortion maintaining placental viability for secondary placental implantation on the uterus and broad ligament. The left fallopian tube and ovary were normal and uninvolved, and the right fallopian tube had been removed previously.

Advanced abdominal pregnancy should be suspected in cases of hemoperitoneum, abnormal presentations, feath death, spurious labor, and a history of infertility, prior tubal operation, or threatened abortion. The management is an individualized operation as soon as the diagnosis is made and adequate blood replacement is available.

All cases of hemoperitoneum, with or without a subtle menstrual irregularity, should have a determination of serum β–human chorionic gonadotropin to aid in the diagnosis of early abdominal pregnancy.

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Discussion

DR. THOMAS K. GRIFFITH, Corvallis, Oregon. It is said that less than 50% of advanced abdominal pregnancies are diagnosed as such prior to laparotomy. I commend Drs. Hallatt and Grove for bringing our attention once again to this rather uncommon condition, for to diagnose abdominal pregnancy, we must think abdominal pregnancy. Ideal obstetric management of this potentially lethal problem implies early diagnosis and prompt intervention, but the authors have demonstrated the difficulties in establishing an accurate and early diagnosis. One cannot overemphasize the importance of establishing early prenatal care and maintaining an aggressive approach to correct diagnosis in suspected ectopic gestation, if the risks of advanced abdominal pregnancy are to be avoided.

Advanced abdominal pregnancy truly presents a formidable challenge to the most skilled clinician. A maternal mortality rate of 6% to 14% has been reported, and the maternal morbidity associated with this condition may be awesome. Not uncommon are case reports that describe maternal clotting disorders, catastrophic intraoperative bleeding from placental separation, postoperative bowel fistulas, and postoperative sepsis that persists for months. The fetus fares no better, as this present study demonstrates. Perinatal mortality rate averages 75%. The surviving infants experience a 30% to 90% chance of serious congenital malformation, generally related to oligohydramnios.

Drs. Hallatt and Grove have categorized some of the signs and symptoms of late abdominal pregnancy, but none is diagnostic. A review of the literature hints that pain is a fairly constant feature of this disease. In particular, painful fetal movements should alert one to the possibility of an extrauterine pregnancy. Abdominal pregnancy should also be considered in the evaluation of an unexplained antepartum death. Pelvic examination in abdominal pregnancy may show displacement of the cervix from its usual position. Several authors emphasized the observation that the "uterus" fails to contract under the influence of oxytocin. This, however, is not a consistent finding. Diagnostic criteria for x-ray and ultrasound examinations have also been established, but these too are not infallible.

In their final statement, Drs. Hallatt and Grove urge prompt surgical intervention when a diagnosis of advanced abdominal pregnancy has been made. The risk of an intra-abdominal catastrophe does not allow for a period of watchful waiting, nor does the high fetal mortality and malformation rate warrant delay for fetal indications. At operation, and after removal of the fetus, the clinician must make a decision concerning the fate of the placenta. Postoperative maternal morbidity will probably be lessened by removal of the placenta, if this is technically feasible. If the vascular attachments involve major vessels or vital structures, the organ should be left undisturbed. If intractable abdominal bleeding is encountered, the use of a gravity suit with circumferential abdominal pressure may be lifesaving.

Finally, some authors think that the maternal morbidity and mortality associated with the retained placenta may be lessened by the administration of methotrexate to the postoperative patient. Others have abandoned this approach, fearing the toxicity of the drug far outweighs its usefulness. I would like to ask Drs. Hallatt and Grove whether their group has had any experience with the use of methotrexate in this context.

Dr. Hallatt (Closing). I want to thank Dr. Griffith for his concise description of the management which I largely neglected because I was dealing more with the pathophysiology of abdominal pregnancy. As for his question in regard to the use of methotrexate, we have not used methotrexate because we strongly believe that, as soon as the diagnosis of abdominal pregnancy is made, surgical intervention is indicated. One might pause long enough to consider a bowel preparation; one might consider the use of prophylactic antibiotics and certainly the availability of adequate blood replacement. I am glad he brought up the point about the Mast suit. This truly must be a lifesaving procedure. We have used it on one occasion, and Dr. Eugene Sandberg, of our Society, has pointed out the valuable aspects of the use of the Mast suit.

Water-soluble radiocontrast material in the treatment of postoperative ileus

Dean T. Watkins, M.D., and Charles L. Robertson, M.D.
Boise, Idaho

Reviewed was a series of 47 obstetric, gynecologic, and general surgical patients with apparent postoperative ileus who had received an oral administration of water-soluble radiocontrast material. Forty of these patients were found to have an ileus, and seven to have a mechanical small bowel obstruction. In the 40 patients with ileus, prompt resolution of the ileus was obtained, no complications were noted, and the method provided rapid differentiation between ileus and obstruction. This modality of therapy offers an excellent alternative both therapeutically and diagnostically to the traditional treatment of ileus with intravenous fluid, nasogastric suction, and gastrointestinal rest. (AM J OBSTET GYNECOL 1985;152:450-5.)

Key words: Ileus, postoperative abdominal distention, water-soluble radiocontrast material

Abdominal distention in the postoperative patient is a dilemma. In order to secure the patient's comfort and safety, and for economic reasons, differentiation of ileus from obstruction is essential. Cowley and Vanley,[1] in 1965, presented six cases of the therapeutic use of water-soluble radiocontrast material, but little has appeared in the literature concerning this valuable modality since that time. For the past 12 years, the radiologists and several surgeons at St. Luke's Regional Medical Center have used water-soluble radiocontrast material to differentiate ileus from obstruction. Prompt resolution of ileus was noticed in numerous patients. This article reports that experience.

Material and methods

This retrospective study was conducted at St. Luke's Regional Medical Center, a 350 bed general hospital in Boise, Idaho. Forty-seven postoperative cases which met our criteria were selected in chronologic sequence, representing approximately 2 years of experience. These patients had had a variety of intra-abdominal procedures (Table I). All patients with intestinal anastomoses were excluded, except two with gastric stapling. Those studied ranged in age from 24 hours to 87 years. The diagnosis of ileus and/or possible mechanical obstruction was a clinical and radiographic one and varied somewhat because of the number of clinicians and radiologists involved.

Table I. Types of surgical procedures studied and the number of cases of each type

Type of surgical procedure	*No. of cases*
Abdominal hysterectomy	6
Abdominal hysterectomy with bilateral salpingo-oophorectomy	10
Vaginal hysterectomy with anterior and posterior repair	1
Cesarean section	5
Abdominal hysterectomy with Marshall-Marchetti-Kranz procedure	2
Bilateral salpingo-oophorectomy	1
Exploratory laparotomy	2
Gastric bypass	2
Appendectomy	4
Herniorrhaphy	2
Aortic graft	3
Ureterolithotomy	1
Cholecystectomy	5
Nephrectomy	1
Lysis of adhesions	1
Repair of peritoneal rent from umbilical artery cutdown	1

After preliminary supine and erect abdominal films had been obtained, 120 ml of diatrizoate meglimine or diatrizoate sodium (Gastrografin or Gastroview) was administered orally or via nasogastric tube to adult patients and a proportionately smaller dose was administered to children and to newborn infants. The osmolarity of this undiluted contrast material is approximately six times[2] that of extracellular fluid and can be expected to draw significant amounts of fluid from the intravascular space and extracellular space into the gastrointestinal lumen.[3] An arbitrary film sequence at 1, 3, and 6 hours was performed in most patients, with a 24-hour film being obtained whenever necessary.

The parameters studied included: (1) interim from operation to the time of study, (2) approximate dura-

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Table II. Parameters of ileus studied

	Average	*Range*
Interim from operation to the time of study	4.2 days	2 to 14 days
Approximate duration of ileus	35 hr	12 to 96 hr
Transit time from ingestion to large bowel	3 hr 20 min	25 min to 6 hr
Transit time from ingestion to first stool	6 hr 20 min	1 to 18 hr
Duration of hospitalization after study	3.8 days	1 to 8 days
Obstetric-gynecologic patients	2.8 days	1 to 7 days

tion of ileus, (3) transit time from ingestion to large bowel, (4) transit time from ingestion to first stool, and (5) duration of hospitalization after the study.

Results

Forty-seven consecutive cases were reviewed, and 40 patients were determined to have hypodynamic or paralytic ileus. These results are summarized in Table II. Transit time from ingestion of contrast material to passage into the large bowel averaged 3 hours and 20 minutes, with a range of 25 minutes to 6 hours, and the average time from ingestion to first stool was 6 hours and 20 minutes. The first stool after ingestion of contrast material was typically watery and voluminous, and in most patients was followed by two to four other bowel movements.

Length of hospitalization after ingestion of contrast material averaged 3.8 days, with a range from 1 to 8 days. In obstetric and gynecologic patients, an average of 2.8 days was noted.

Figs. 1 through 3 demonstrate a typical sequence of events in the usual case of ileus. Fig. 1 is a plain film that shows a typical ileus. Fig. 2 is a 3-hour postingestion radiograph that demonstrates passage of contrast into the colon. Fig. 3 is a 6-hour postingestion film that demonstrates material in the rectum in a patient who had had a recent first stool after ingesting contrast material.

Figs. 4, 5, and 6 demonstrate an occasional finding that is worth reporting. This is the resolution of a small bowel obstruction apparently by small bowel hypermotility produced by the contrast material.

Case report

V. W. was a 75-year-old white woman who on the eleventh postoperative day required readmission because of vomiting, abdominal distention, and the inability to retain oral fluid. Eleven days previously, she had undergone an exploratory laparotomy with lysis of adhesions for mechanical small bowel obstruction. Fig. 4 shows the plain film taken on the day of admission, with dilated loops of small bowel that suggest obstruction. Fig. 5, a film taken 3 hours after ingestion of contrast material, indicates passage of the contrast material into the colon. Within 4 hours of ingestion, this patient had her first stool. Fig. 6 is a delayed radiograph taken 16 hours after ingestion and demonstrates complete resolution of the small bowel obstruction. The patient was discharged home on the fourth postadmission day; she did not require reexploration, and recovered uneventfully.

Comment

In the management of postoperative abdominal distention, plain films of the abdomen are helpful but are often not definitive. Barium sulfate is potentially dangerous because of the hazard of free peritoneal barium if perforation occurs or is present. Furthermore, barium is not of apparent therapeutic value.

Water-soluble contrast material, unlike barium, is nontoxic if accidentally introduced into the peritoneal cavity. In fact, intraperitoneal contrast material can be intentionally used, as in peritoneography or herniography.[4] The hyperosmolar water-soluble contrast material draws fluid into the intestinal lumen and appears to act as a direct stimulant to intestinal peristalsis.

In patients with ileus, passage of liquid stool and flatus was noted within a few hours. In all patients with ileus, oral alimentation was reestablished within 24 hours of passage of stool and gas.

No complications were noted in this series of 47 cases. One patient developed paroxysmal atrial tachycardia approximately 24 hours after ingestion of contrast material, but this was thought not to be related to the procedure. It has been suggested that water-soluble contrast material is contraindicated for the evaluation of suspected small bowel obstruction because of the possibility of shock produced by increased intraluminal volume. Although movement of fluid from the intravascular and extracellular spaces into the lumen of the gut may be hemodynamically significant and potentially needs to be corrected with intravenous fluid, we have not found this to be a problem and think that the potential benefit from definitive diagnosis of mechanical obstruction outweighs the potential risk. Oral contrast material should probably be avoided in patients who are obtunded or vomiting, since aspiration of contrast material could result in pulmonary edema.[5]

Water-soluble contrast material does not afford the same mucosal detail that can be demonstrated with the use of barium as the contrast agent.[6] This may account for the general reluctance of radiologists to use water-soluble contrast material. However, in this group of

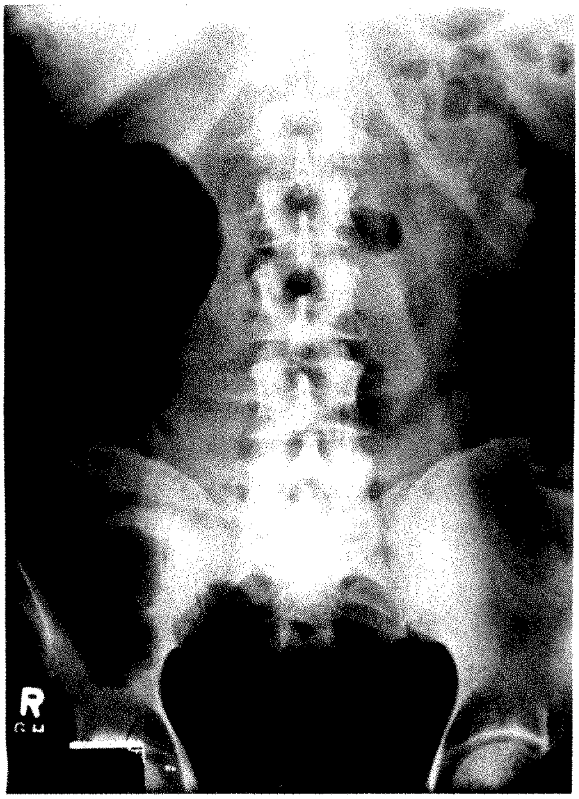

Fig. 1. Open film demonstrating typical ileus.

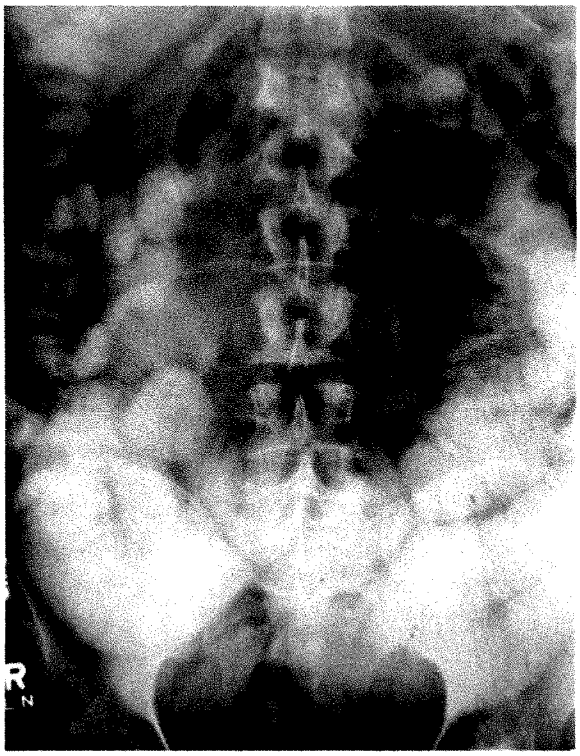

Fig. 2. Radiograph taken 3 hours after ingestion of contrast material showing passage of the contrast material into the colon.

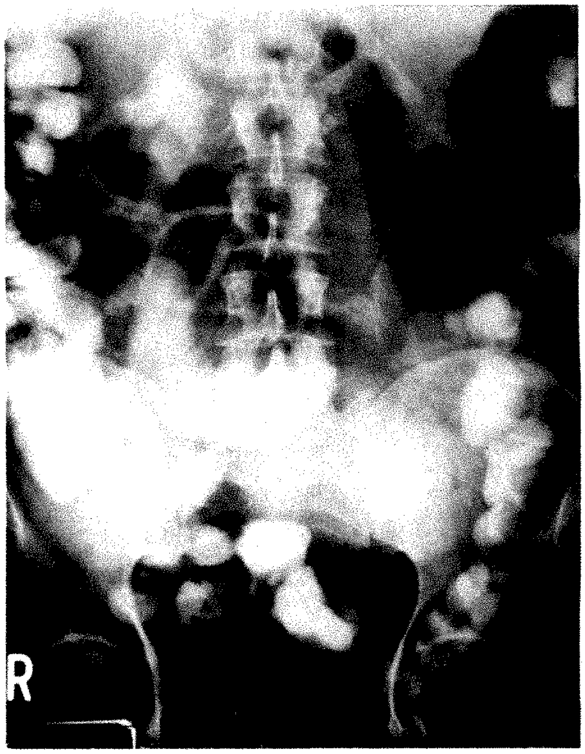

Fig. 3. Film 6 hours after ingestion of contrast material shows passage of the material through the colon.

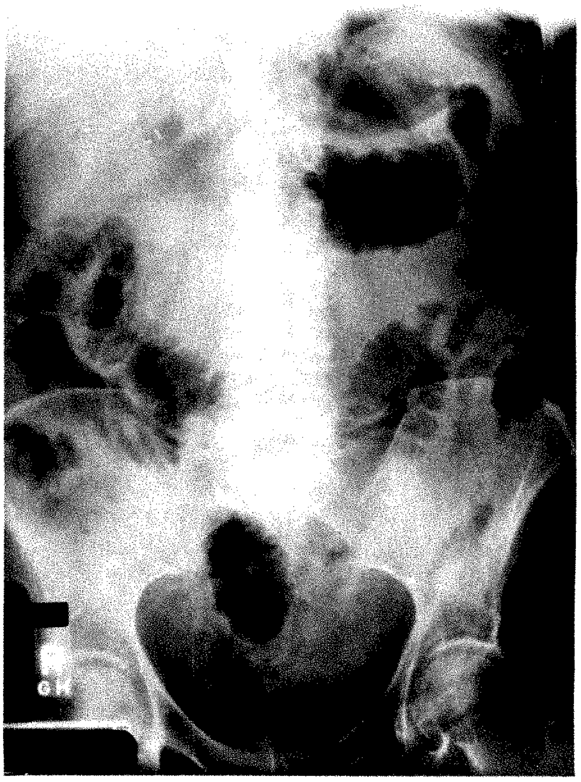

Fig. 4. Open film diagnosed as small bowel obstruction.

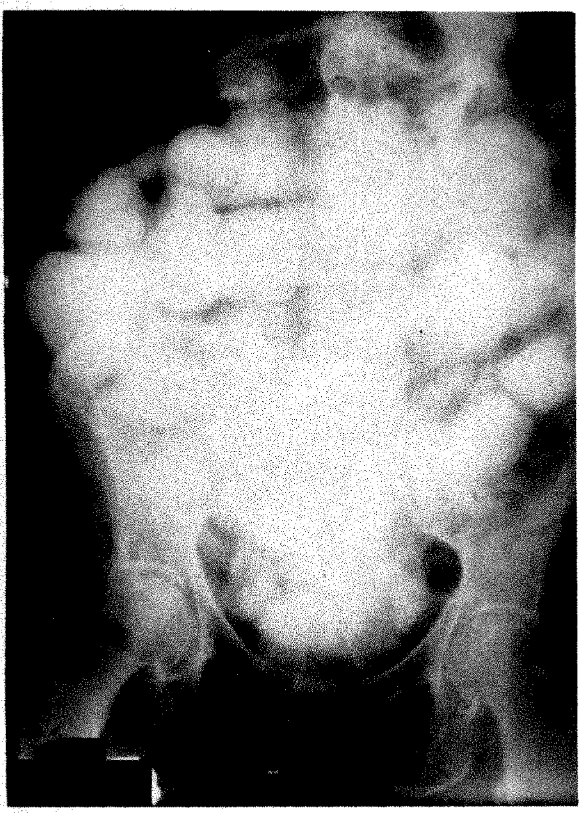

Fig. 5. Film taken 3 hours after ingestion of contrast material showing passage of the material into the colon.

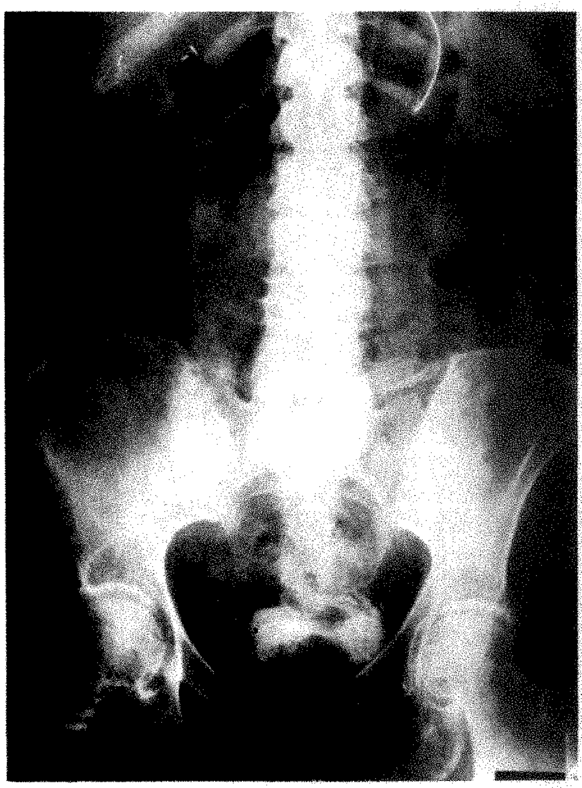

Fig. 6. Delayed radiograph taken 16 hours after ingestion of contrast material showing complete resolution of the small bowel obstruction.

patients, mucosal detail is not paramount, but the differentiation of ileus from obstruction is of primary importance. Furthermore, the therapeutic effect of water-soluble contrast material in patients with ileus is not generally observed with the use of barium.

Patients with bowel resection were intentionally excluded from this study, but many such cases have been studied in our institution without deleterious effect. Extravasation at the site of anastomosis, in fact, would be a desirable observation if an anastomotic leak were present, since detection and surgical repair of such a leak would be clinically important.

With the rapid resolution of the ileus and the attendant decrease in abdominal distention, the patient's comfort is significantly enhanced. Furthermore, prompt resolution of the problem, with an apparent decrease in the expected length of stay in the hospital, is increasingly important because of the high cost of medical care.

In summary, we have found the use of water-soluble radiocontrast material in the patient with postoperative distention to be effective, inexpensive, safe, and reliable. It has received little attention in the literature, and we hope this review may stimulate interest in the use of this simple yet highly effective procedure.

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Discussion

Dr. Gilbert A. Webb, San Francisco, California. Drs. Watkins and Robertson presented 47 consecutive cases, with 40 patients having postoperative paralytic ileus and seven having ileus due to mechanical obstruction. This was demonstrated by the use of diatrizoate meglimine or diatrizoate sodium (Gastrografin or Gastroview). The authors apparently had 100% accuracy in the diagnosis, which is in sharp contrast to the experience of Zer et al.,[1] who had only a 70% reliability.

They also quote Sufian and Matsumoto as having only a 50% reliability.

Zer et al. did not refer to the use of these agents as therapeutic but only as diagnostic. However, they used only 30 to 40 ml of Gastrografin, whereas I note that Drs. Watkins and Robertson used 120 ml. I would ask them why they chose this dosage? Since these agents are extremely hyperosmolar, drawing large quantities of fluid into the lumen of the bowel and causing rapid distention of the obstructed bowel, use of them may occasionally result in iatrogenic intestinal perforation according to Ott and Gelfand.[2] This would be more likely to occur with the large dose. The latter authors also point out that these agents may have an irritant effect on the gastrointestinal mucosa, especially if stasis or obstruction causes prolonged retention in a viscus. They state that this irritant effect has occasionally led to severe gastric or colonic hemorrhage, with precipitation of these agents, or a direct toxic effect, with these ingredients presumed to be responsible. Fortunately, these complications are uncommon.

Zer et al. have used Gastrografin to correct ileus due to impaction of hardened residual barium stagnated in the colon, a rare complication of barium meal examinations,[3] but one that constitutes a particularly serious problem when it occurs after abdominal operations that lead to ileus. Drs. Watkins and Robertson apparently had no complications in their series of 47 cases and have certainly had an excellent rapid resolution of the paralytic ileus in the 40 cases that they presented in detail. I would like to ask them the nature of the seven cases when obstruction was diagnosed? I also note that they used this in one or more newborn infants. Since these agents have been effective in the dissolution of meconium ileus, I would like to ask what condition necessitated the use of them in the newborn infants in this series. Bar-Maor et al.[4] found Gastrografin to be effective in the relief of subacute intestinal obstruction due to *Ascaris lumbricoides* in children. I wonder whether Drs. Watkins and Robertson had occasion to use these agents for this condition, since this infestation has been noted in Southeast Asian immigrants.

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Dr. Keith Russell, Los Angeles, California. As a proponent of early ambulation, early feeding, and indwelling urethral catheters for the uncomplicated gynecologic surgical case, I would have to suggest that Drs. Watkins and Robertson's 100% failed results are not from the water-soluble contrast material, as much as from not putting something in the bowel. Most ileus comes about from excess handling of the bowel or from excessive packing. I do not mean to criticize our good friends from Boise, especially the general surgeons, for somewhat rough handling of tissues, large bites of tissue, and suturing and cutting and so forth. I think that the prevention methods available are better than the treatment. Experience has shown that early ambulation or early feeding will be helpful in returning to normal the patient with an uncomplicated gynecologic condition. This means that a patient must get out of bed on the evening of the operation, avoid the standing order of nothing orally for 24 or 48 hours, discontinue intravenous fluid, which contributes to the patient's discomfort, go to the bathroom that evening with help, and be on a soft diet the morning after the operation. I emphasize that this is for the average gynecologic patient whom we see. Surgeons often deal with bowel problems in their work, and they treat all cases as though they were bowel problems. Our work seldom includes excessive dissection that involves the bowel. We involve the bowel by packing it off excessively or by handling it. For instance, one of the things taught in my own institution is to take the uterus out of the abdomen when closing the uterus after a cesarean section. I see no reason for that. All that accomplishes is exteriorization of an organ that is normally within the abdomen. I may be roiling the waters, but this concept which is supported in the surgical literature is largely ignored by most of us because we are all traditionalists.

Dr. Enrique de Castro, Portland, Oregon. This report by Drs. Watkins and Robertson is instructional and of great importance to all clinicians. Approximately a year ago, we had two patients who developed so-called ileus. For the first time, the use of Gastrografin was introduced. These two cases resolved very quickly and we had the patients out of the hospital in a very short time. This prompted me to research this as a useful treatment. I am happy that Drs. Watkins and Robertson presented this report. We often come to these meetings and listen to various discussions about subjects that we think do not pertain to our clinical practice, and then, as soon as we go back to our offices, we find the problem presenting itself. I think that it is important to remember Gastrografin. It may be very helpful and should be investigated in our own institutions. Dr. Russell's comments are appreciated, and I do agree with him that some patients will develop an ileus regardless of whether we feed them early or late. We generally accept early ambulation and early ingestion of liquids. In those patients who do develop an ileus, I think the use of Gastrografin will be a great aid.

Dr. William Lucas, San Diego, Califronia. I would like to add a little to what Dr. de Castro said. I was delighted to hear Drs. Watkins and Robertson's report because my spectrum of practice may be a bit different from that of Dr. Russell. I had an ongoing battle with our radiologist for about 10 years because he did not like to use Gastrografin. He preferred to use barium, which they call "thin barium," and which can, in my experience, lead to disaster. We have had no problems from the alleged toxicity and frequently have found it to be very helpful, not so much therapeutically but diagnostically. I think that several points can be made. One is that a small tube can be introduced fluoroscopically into the upper small bowel and Gastrografin can be introduced through the tube and the progress of the Gastrografin can be followed fluoroscopically. This has provided the advantage of our being able to pinpoint transit time and to localize the site of obstruction. Also, we get a pretty good idea of the degree of obstruction, as was already pointed out by Dr. Webb. I believe partial obstruction may still necessitate surgical intervention. Again, I think that this report has been an important contribution, and that the use of water-soluble radiocontrast material should be in our therapeutic regimen.

Dr. Simon Henderson, San Francisco, California. I most appreciated Dr. Russell's remarks about handling the bowel. I think that this is one of the main reasons for ileus. I believe that allowing some blood and clots to remain in the abdomen is usually unavoidable. This can lead to ileus. About 7 or 8 years ago, the use of dextrans was suggested for preventing the formation of adhesions in the abdomen. I have been using Macrodex (dextran 70) in a 6% solution and use it to wash the abdomen after any gynecologic procedure. I do many tubal operations which entail the removal of bowel from the adnexa. I handle the bowel quite extensively in such cases. In these patients, ileus would be expected to develop, as it would in patients who undergo myomectomy, with which there is postoperative bleeding. In these operations, I have been leaving approximately 100 to 200 ml of dextran 70, 6%, in the abdomen, and I am absolutely amazed that we have not had a problem with ileus in these patients.

Dr. Watkins (Closing). Dr. Henderson, the idea of the use of Macrodex is a very interesting one. One of our partners does perform many microsurgical tubal procedures and is really pushing that. Dr. Lucas, we have not used the feeding tube and the deposition of Gastrografin into the small bowel. That is a very interesting idea and very helpful, I am sure. I want to thank Dr. de Castro for his comments. Dr. Russell, the gynecologists in Boise are extremely gentle with tissues, but you will notice that I had to include many general surgical and urologic cases to obtain a fair number of patients. I want to respond to Dr. Webb's specific questions in the following way. I recognize that it takes a great deal of courage to present this particular subject. I understand that a radiologist in California has written in a standard text on radiology that radiographin is contraindicated. Robert Standley, at the University of Alabama at Birmingham, has used this for many years and has not written of his experience. My co-worker, Dr. Robertson, a senior radiologist at St. Luke's Regional Medical Center, has used this in probably a thousand cases, and simply does not have any problem with the procedure. The largest series that I found in the literature of the therapeutic use of this was the one reported by Cowley and Vanley, in 1965, and they had six cases, so that our series of 47 cases is significantly larger. How do we get 100% success? Anything that appears to be "too good to be true" probably is. The seven cases of obstruction were cases of total obstruction, and in all of them reexploration was required. The 40 cases that we classified as ileus resolved, and alimentation was reestablished within 24 hours. I think that some of these patients must have had mild obstruction rather than a simple ileus. You commented on the amount of contrast material used. The product information brochure suggests 30 to 99 ml. This is diagnostic. We have used 120 ml because we were using it in a therapeutic way. Toxicity may be a problem. If the material gets into the lungs, it will cause pulmonary edema. The 24-hour-old patient was an infant who had an umbilical catheter and a possible necrotizing enterocolitis. The radiologist passed the contrast material through a nasogastric feeding tube to differentiate obstruction secondary to an ischemic lesion from ileus. I do not know how to explain the other report in which the authors noted transit in 30 to 90 minutes. I have seen patients have multiple stools within 30 minutes. As for the question about length of stay, 2.8 days is the usual time for obstetric-gynecologic patients. This is relatively prompt dismissal when one considers the nasogastric tube, orders for no oral intake, and restarting intravenous fluid. With our method, the problem is resolved within 4 to 6 hours.

Adnexal torsion

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A series of 128 cases of adnexal torsion and an additional 97 cases where the preoperative diagnosis of torsion was incorrect are reviewed. The diagnosis is uncertain and surgical intervention is likely to be delayed. The adnexa are seldom salvaged despite the fact that torsion infrequently involves a malignant neoplasm. Laparoscopy is an effective means of reducing the number of necessary laparotomies when a diagnosis of torsion is uncertain. (AM J OBSTET GYNECOL 1985;152:456-61.)

Key words: Ovary, tube, torsion

Adnexal torsion is a well-known, poorly recognized, and infrequently encountered clinical entity that can involve the tube, ovary, and ancillary structures either separately or together. Because there is little recent information on this subject,[1-5] a 10-year experience with adnexal torsion at a large metropolitan hospital is surveyed.

Material

During the 10-year period ending December 31, 1983, a total of 3772 patients requiring an emergency operative procedure were treated at Women's Hospital (Table I). Adnexal torsion was the fifth most common condition encountered, there being 102 cases or 2.7% of gynecologic surgical emergencies. In addition there were 26 cases of torsion with infarction discovered at the time of an elective operation and 97 other patients who had an erroneous preoperative diagnosis of torsion, giving a total of 225 cases for study.

The patient population at Women's Hospital is either self-referred or physician referred, usually because of financial considerations, and consists of a broad range of ages with the exception of the pediatric group, which is somewhat underrepresented. According to Adelman et al.,[6] approximately 15% of adnexal torsion occurs during infancy or childhood and the majority of these cases do not involve either a tumor or a cyst.

As has been reported in other series, the most likely cause of torsion was a benign cystic ovarian tumor. However, more than half (52%) of torsions did not involve an ovarian neoplasm; these included 23 cases (18%) where no specific lesion could be identified.

The operative findings are listed in Table II. Among the 102 emergency and 26 elective cases, 85 (66%) of torsions occurred in the right adnexal structures and none were bilateral.[7] In keeping with its frequency, the most common neoplasm to undergo torsion was a dermoid cyst. However, the risk of torsion for a dermoid cyst was less than that for several other common lesions. As calculated in Table III, paraovarian (or paratubal) cysts, solid benign tumors, and serous cysts were all at a greater risk of torsion. There were 27 instances of torsion of tube or ovary, of which 23 were not associated with an identifiable lesion. In three cases an ovary was described as being "polycystic" and in one case the tube apparently had contained a hydrosalpinx. The average age of these 27 patients was 29 and the oldest patient was 54.

Of considerable interest was the fact that only two cases involved a malignant ovarian neoplasm. One 19-year-old individual had a borderline serous cystadenocarcinoma treated by unilateral salpingo-oophorectomy; and the other patient, aged 44, had a Stage IA serous cystadenocarcinoma treated by total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. This last patient received chemotherapy and is without evidence of disease 5 years following operation. For both cases, the preoperative diagnosis of torsion had been made. On the basis of our experience, the risk of torsion for a malignant ovarian neoplasm is 2.4% (two of 81 cases) as compared to a risk for benign neoplasms of 11% (59 of 516 cases); and the risk that a given adnexal torsion involves a malignancy is 1.6%. By way of contrast, Lee and Welch[4] have reported that 20 of 135 patients (15%) treated for adnexal torsion at Mayo Clinic had an ovarian malignancy. Perhaps this disparity is explained by the fact that 27% of the Mayo Clinic patients were postmenopausal as compared to 4.5% in this series.

Bearing in mind that the size of a twisted adnexal lesion is considerably increased by hemorrhage and edema, it was estimated that most of the tumors and cysts appeared to have been of moderate size. None

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Table I. Surgical emergencies: 1974-83

Diagnosis	*No. of cases*
Ectopic pregnancy	2407
Corpus luteum accident	546
Pelvic infection	342
Appendicitis	180
Adnexal torsion	102 (2.7%)
Uterine perforation	49
Other	90
Total	3772

Table II. Adnexal torsion: operative findings

Neoplasms		62 (48%)
Dermoid cyst	38	
Serous adenoma	12	
Serous carcinoma	2	
Mucinous adenoma	6	
Fibroma/thecoma	4	
Struma ovarii	1	
Hemangioma	1	
Cysts		39 (31%)
Parovarian	24	
Corpus luteum	7	
Serous	6	
Endometrioma	2	
Site		27 (21%)
Tube	6	
Ovary	12	
Tube and ovary	9	
Total		128 (100%)

were ruptured or infected. In 33 of 42 cases (80%) where an ovary was not directly involved in the twisted pedicle, there was sufficient impairment of its blood supply to require an oophorectomy.

Table III. Risk of torsion

Lesion	*Risk ratio*
Parovarian cysts (n = 124)	1:5
Solid benign tumor (n = 29)	1:6
Serous cyst (n = 85)	1:7
Dermoid cyst (n = 344)	1:9
Mucinous cyst (n = 79)	1:13

Table IV. Adnexal torsion: Preoperative diagnosis

Torsion		85
Incorrect diagnosis		43
Adnexal mass	21	
Appendicitis	8	
Pelvic mass	7	
Myoma	3	
Ectopic pregnancy	2	
Abscess	1	
Ruptured viscus	1	
Total		128

Table V. Numbers with incorrect preoperative diagnosis of torsion

Correct diagnosis	*No.*
Corpus luteum accident	24
Tuboovarian abscess	22
Hydrosalpinx	9
Appendicitis	8
Endometrioma	7
Salpingitis	6
No disease	5
Ectopic pregnancy	4
Myoma	4
Tuberculosis	3
Ruptured ovarian neoplasm	2
Ovarian cancer	1
Diverticulitis	1
Small bowel obstruction	1
	97

Diagnosis

A number of authors have attempted to simplify the problem of diagnosis by identifying clinical features typical of torsion. There is general agreement that the majority of patients will experience some type of pain and will have a palpable adnexal mass. Nausea and vomiting following the onset of pain is fairly common and there is apt to be moderate leukocytosis associated with minimal fever. A substantial percentage of patients will have been symptomatic for a number of days both before consulting a physician and before a physician takes action. Perhaps 10% of patients had experienced intermittent torsion over a period of time, as suggested by a history of repeated attacks of pain interspersed with asymptomatic intervals. Although these patients fit into the above description, the difficulties in arriving at a precise diagnosis are well illustrated by errors in preoperative diagnosis. If only patients with a demonstrated torsion are considered, the diagnostic accuracy was 85 of 128 cases, or 66%. When patients with a preoperative diagnosis of torsion who subsequently proved to have some other condition are added to the total, the diagnostic accuracy was 85 of 225 cases, or 37.8%.

An inability to accurately recognize torsion is reflected in the number and variety of gynecologic conditions with which it is confused. In Table IV are listed 43 cases with proved adnexal torsion but an incorrect preoperative diagnosis. Forty-two of these 43 patients had an operative finding grossly consistent with infarction despite the fact that only 12 had sufficient signs and symptoms to inspire a diagnosis of an emergent surgical process. The remaining 31 patients were found to have an unsuspected torsion and infarction at the time of an elective operation for a presumptive diagnosis of a tumor or a cyst that had been accompanied by minimal and unimpressive amounts of pain, discomfort, or tenderness.

Those patients thought to have adnexal torsion and who proved to have some other process are listed in

Table VI. Risk of incorrect preoperative diagnosis of torsion

Correct diagnosis	*Risk rate*
Ruptured ovarian neoplasm (n = 4)	1:2
Pelvic tuberculosis (n = 13)	1:4
Small bowel obstruction (n = 4)	1:4
No disease (n = 24)	1:5
Acute salpingitis (n = 29)	1:5
Diverticulitis (n = 7)	1:7
Endometrioma (n = 89)	1:13
Tuboovarian abscess (n = 282)	1:13
Appendicitis (n = 170)	1:17
Corpus luteum accident (n = 496)	1:21
Hydrosalpinx (n = 448)	1:76
Ovarian cancer (n = 79)	1:79
Uterine myoma (n = 1437)	1:360
Ectopic pregnancy (n = 2407)	1:601
Average	1:58

Table VII. Torsion: Results of laparoscopy

Preoperative diagnosis	*No.*	*Postoperative diagnosis*	*No.*
Torsion	4	Torsion	1
Adnexal mass	1	Torsion	4
Torsion	27	Corpus luteum accident	9
		Tuboovarian abscess	6
		No disease	4
		Salpingitis	3
		Hydrosalpinx	3
		Ectopic pregnancy	1
		Appendicitis	1
Total			32

Table V. Most of the misdiagnoses involve either infection (40) or hemorrhage (35)—with almost half being due to either a corpus luteum accident or tuboovarian abscess. When the risk of mistaking various surgical conditions for adnexal torsion is calculated (Table VI), it can be seen that, with the exception of salpingitis, errors in diagnosis are more likely for those surgical problems seldom encountered by the gynecologist and are relatively uncommon for familiar diseases.

Ancillary tests did not play a prominent role in the diagnosis of adnexal torsion. An abdominal x-ray film identified the characteristic radiologic findings of seven dermoid cysts. For eight other dermoid cysts plus an additional 22 cases, an x-ray film served only to confirm the presence of a mass that was already clinically evident. Ultrasonography was used in 14 cases and served principally to confirm the presence of a palpable mass and, in most cases, to demonstrate that it was cystic. In one case, a twisted parovarian cyst could be identified preoperatively because a mass separate from the adjacent ovary could be identified by an ultrasonic scan.

Table VIII. Torsion: Operations

	No. of cases	*%*
Salpingo-oophorectomy	89	69.5
Oophorectomy	14	11
Cystectomy	9	7
Hysterectomy, salpingo-oophorectomy	16	12.5
Total	128	100
Appendectomy	8	
Cystectomy (opposite ovary)	9	

Table IX. Adnexal torsion in pregnancy

Lesion	*Nonpregnant patient*	*Pregnant patient*
Benign neoplasm	49	12
Ovarian cyst	9	4
Parovarian cyst	20	4
Tube/ovary	24	3
Other	5	—
Total	105	23

Laparoscopy was used to establish a diagnosis for five patients who proved to have torsion and an additional 27 patients who had some other condition. As seen in Table VII, a correct preoperative diagnosis of torsion was made for four patients (three of whom were pregnent), and one unsuspected case of torsion was discovered. Laparoscopy was of considerable value in ruling out a presumptive diagnosis of torsion and was instrumental in avoiding a laparotomy for 19 of 27 patients who did not have an adnexal torsion.

Culdocentesis was used in only 11 patients with torsion, probably because of the fear of puncturing a tumor or abscess. In seven of these 11 cases, the demonstration of blood-tinged fluid was supportive of a diagnosis of torsion. Pregnancy tests were frequently used but were of limited value because 18% of patients with adnexal torsion also had an intrauterine pregnancy.

Treatment

Because most patients with adnexal torsion are relatively young (average age of 26 in this series), preservation of tubes and ovaries is an important objective. With early diagnosis and treatment it might be possible to conserve normal structures by untwisting the pedicle and resecting cysts or tumors, when applicable, as has been suggested by Way.[8] Unfortunately, in the majority of cases the operation was sufficiently delayed so that it was not possible to differentiate by inspection alone between necrosis and strangulation. Most surgeons were reluctant to untwist the pedicle because of the fear of releasing an embolus from a thrombotic vein. As a result, few adnexa were salvaged.

The operative procedures used in this series are listed in Table VIII. Only nine ovaries were preserved: those from six cases where the torsion involved a parovarian cyst, two cases involving a dermoid cyst, and one case involving a mucinous cystadenoma. The opposite ovary was resected because of bilateral dermoid cysts (four), endometriosis (one), or a parovarian cyst (three). The indications for hysterectomy were age 45 or over (10), elective sterilization (three), infected dermoid cyst (one), endometriosis (one), and ovarian carcinoma (one).

Eight appendectomies were performed, including five elective operations and three cases where the torsion was not discovered until after an appendix had been removed for the preoperative diagnosis of appendicitis. This relatively small number of elective appendectomies is in keeping with a growing reluctance among gynecologists to perform this procedure and can be contrasted with the statement of Lee and Welch, in 1967,[2] that in the Mayo Clinic experience "the appendix, if present, was generally removed."

Complications

Because adnexal torsion is largely confined to young women, usually requires a simple operation, and seldom involves gross infection or a major blood loss, the operative and postoperative complications are minimal and recovery is rapid. The only complications encountered in this series was a modest amount of ileus, atelectasis, and urinary tract infection. In particular, no patient suffered a pulmonary embolus from a thrombosed ovarian vessel and there were no ureteral injuries and no instance where the ureter was drawn up into a twisted pedicle. The real complication for 60% to 70% of these patients with torsion was the loss of a functioning and potentially salvageable ovary.

Pregnancy

Twenty-three (18%) of the patients had an intrauterine pregnancy, including 16 patients between the sixth and thirteenth week and seven patients between the fourteenth and twenty-second week. No torsions were encountered in the third trimester. With the possible exception of a higher incidence of an involved corpus luteum cyst, torsions in pregnant patients are quite similar to those in nonpregnant patients (Table IX). The problems of diagnosis are also similar. In pregnant patients, 70% of torsions were diagnosed preoperatively as compared to 66% in nonpregnant patients. Both of the patients with an erroneous preoperative diagnosis of ectopic pregnancy had an intrauterine pregnancy along with adnexal torsion. Of six pregnant patients having an incorrect preoperative diagnosis of torsion, three proved to have a degenerating myoma, two had a ruptured corpus luteum cyst, and one had appendicitis.

Comment

If it were to be assumed that the results observed at Women's Hospital are the common experience, the following conclusions could be drawn:

1. Adnexal torsion is uncommon, but not rare, and needs to be considered in the differential diagnosis of a number of surgical emergencies.
2. Because of a lack of impressive symptoms, a number of patients with torsion will undergo an elective operation with some other diagnosis (20%).
3. When torsion is encountered, the odds of making a correct diagnosis are 2 to 1 (85 of 128). When a preoperative diagnosis of torsion is made, the odds that it will be correct are 2 to 3 (85 of 225). A coexisting pregnancy shortens these odds.
4. While a dermoid cyst is the most likely lesion to be encountered, a parovarian cyst is the most likely lesion to twist.
5. Adnexal torsion is not likely to be confused with commonly encountered surgical emergencies (such as ectopic pregnancy) but is often confused with less familiar conditions.
6. Torsion of a normal tube or ovary, either single or in combination, is not rare (18% of torsions).
7. If a preoperative diagnosis of torsion is incorrect, one half of the cases will be due to either a ruptured corpus luteum or an ovarian abscess.
8. Few patients with adnexal torsion will have ovarian cancer (2.4%) and few patients with ovarian cancer will be mistakenly identified as having torsion (1.6%).
9. There are few opportunities to salvage an ovary, because of either obvious necrosis, an inability to distinguish between strangulation and necrosis, fear of dislodging an embolus, or a delay in diagnosis because of a lack of convincing symptoms.
10. Adnexal torsion imposes few risks, including that of embolization or ureteral injury.
11. Laparoscopy should be considered if the preoperative diagnosis is unconvincing since a substantial number of laparotomies can thereby be avoided.

In another patient population, the conclusions might be different.

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Discussion

Dr. Charles W. Plows, Anaheim, California. Dr. Hibbard has presented to us a statistical evaluation and discussion of 10 years' experience involving 3772 surgical emergencies. At first glance, 2.7% allotted to torsion of the adnexa would seem insignificant. However, adnexal torsion was No. 5 in the frequency of diagnoses. If one removes the top three diagnoses in Table I (ectopic pregnancy, corpus luteum accidents, and pelvic infection), adnexal torsion becomes a challenge. Indeed, it is found in almost half the number of appendicitis cases. Any disease process which results in the removal of 90% of the involved ovaries deserves the discussion presented by Dr. Hibbard.

Once again, it is obvious that a return to the basics of good gynecologic practices such as a careful history and physical examination, which includes an adequate pelvic examination, is the benchmark for the diagnosis of adnexal torsion. Once diagnosed, it is urgent that immediate therapy be instituted.

As pointed out by Dr. Hibbard, many ancillary tests (flat films of the pelvis, ultrasonography, and culdocentesis) which are used to substantiate the diagnosis when surgical intervention is already planned, are not cost effective. Many times these tests only delay therapy.

Unfortunately, many clinicians are now even further delayed in patient care with onerous third-party restrictions such as preadmission review and prior authorizations, some of which are predicated on extensive outpatient evaluations.

The one modality that appeared to be of significant value in avoiding unnecessary laparotomies was laparoscopy. In Dr. Hibbard's study, 19 of 27 patients were not explored after visualization.

In our hospital, open laparoscopy has become increasingly popular. Since many patients have had previous surgical procedures, we feel more comfortable in introducing the laparoscope under direct vision. Perhaps Dr. Hibbard would care to comment on his experience with the open technique.

With delayed intervention, the hope of salvaging the adnexa is dismal at best. Obviously, early diagnosis must be our goal. At operation, the differentiation between necrosis and strangulation with potential viability is extremely challenging. Since there is no reported cases of bilateral torsion in this study, and with the presence of a normal ovary and tube, safe and swift extirpation of the twisted adnexa seems to be the accepted treatment pattern.

Eighteen patients were treated with hysterectomy because of various indications, including age of 45 or over and elective sterilization. I am sure that these must have been done prior to implementation of the State of California sterilization regulations. Few appendectomies were done. Is it not time that we encouraged appendectomy again at the time of abdominal operation?

Dr. Hibbard's paper alluded to some of the predisposing factors for the occurrence of adnexal torsion. Shapiro et al.[1] reported one of the few cases of torsion of the oviduct following laparoscopic sterilization. It is postulated that tubal sterilization by the burn-and-cut technique decreases the stability of the distal portion of the tube. Moravec et al.[2] reported two cases of torsion of the adnexa in 1980 and related their impressions as to the etiology. Any condition which increases the weight of the fallopian tube, such as pyosalpinx, hematosalpinx, hydrosalpinx, or tubal neoplasms, can predispose to tubal torsion. Sudden body movement associated with exercise (such as aerobics and break dancing) have been associated with adnexal torsion. Uterine enlargement associated with pregnancy or tumors would appear to destabilize the adnexa as the uterus rises out of the pelvis. Pathologic conditions such as endometriomas, inflammatory tuboovarian complexes, and invasive malignant neoplasms would seem to immobilize the adnexa and prevent torsion.

Dr. Hibbard, would you care to comment on actual surgical technique? Should we try to immobilize the adnexa at the time of hysterectomy? What are your impressions about the theory of torsion and de-torsion?

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Dr. Bruce Rolf, Los Angeles, California. I would like to emphasize the latent period that occurs. Often these people are seen with relatively few signs or symptoms, no perceptible mass, and some pain. Two or 3 days later there is infarction and a mass of 8 to 10 cm. I too have a patient who had an endometrial carcinoma within the torsed lesion and I am glad I did not try to untwist it.

Dr. Charles Weber, La Jolla, California. We were taught that in the history of the patient with adnexal torsion there is an element of exertion, exercise or running, that could precipitate such an accident. I am wondering if, in Dr. Hibbard's experience or that of anyone else in the audience, there has been an increase in the incidence of adnexal torsion now that we are living in an age where women are more exercise-oriented?

Dr. Jack Hallatt, Los Angeles, California. I would like to share a case of a twisted tube and ovary in a 13-year-old girl that presented me with a diagnostic and therapeutic dilemma. I would like Dr. Hibbard's opinion as to management. This young lady was hospitalized after suffering from severe abdominal pain for 1 month. When examined, she had a definite, large adnexal mass and needed operation. At operation a 10 cm mass was obvious. A biopsy showed congestion and edema. I thought it might be a neoplasm so I took it out. It proved to be only an edematous tube and ovary. I have no reluctance whatsoever to untwist these tumors. I have never seen pulmonary embolism from untwisting, so I always untwist them in order to evaluate them properly. I believe this tube and ovary, when first twisted, were black and hemorrhagic—what we call necrotic and infarcted. Is there such an entity as a chronic torsion syndrome?

Dr. Edward Hill, San Francisco, California. Dr. Hallatt, I think the case you just described is one of massive edema of the ovary. It has been described by Scully.

Dr. Roger Hoag, Berkeley, California. I wanted to ask Dr. Hibbard how many of his patients had prior tubal ligations. In the last 2 years I have had four cases of torsion of the adnexa in which operation was performed. In three of them the patient had had previous tubal ligations, two laparoscopic and one a Pomeroy tubal ligation. In the cases where the laparoscopic sterilization had been done, it seemed that the remaining portion of the mesosalpinx was very narrow and permitted a twist which then involved the ovary as well. It seemed to me to be odd that you would have 128 cases without a single previous sterilization procedure having been performed in that group.

Dr. Hibbard (Closing). I will take the answers in reverse order. Dr. Hoag, we had one patient who had a torsion of the distal tube following a tubal ligation and three or four other patients who also had previous tubal sterilization. We are dealing with a fairly young group of women. The average age of our patients is 26, so you would expect fewer sterilization procedures. Dr. Hallatt, I would never want to comment on your surgical judgment, which is superb. Is there such a thing as a chronic torsion syndrome? There are patients who have repetitive episodes of torsion and these can do peculiar things. I have one case, not included in this series, of a woman who had evident torsion in the postpartum period. She had bilateral dermoid cysts proved by x-ray film but she was only 2 days post partum and she had had twins. We did not want to operate so we watched her for 24 hours. The pain disappeared and we let her go home. In the next several weeks she had several more episodes of pain, which diminished. Finally, about 6 weeks later, we resected a dermoid cyst on one side and found the usual liquid fatty material in it that you expect. On the other side was fatty material but it was solidified. Dr. Weber, I cannot tell you if exercise makes a difference. Dr. Plows, we do open laparoscopy, which is a fairly recent event because we did not have the equipment before. We now have the special equipment but I find that when our residents perform an emergency laparoscopic procedure, about 25% of the time they do some type of an open procedure. I think open laparoscopy works very well. In our surgical technique, if one is concerned, one can incise the peritoneum along the lateral pelvic wall, to the ovarian vessels, and peel down the posterior leaf of the broad ligament so as to visualize the ureter. This assists in knowing the location of the pedicle that is twisted. As to the numbers that have repetitive episodes of torsion, probably 10% do. I have a feeling that if we questioned these people more thoroughly, we would find a larger percentage actually had torsion and detorsion. Dr. Rolf, yes, there is a substantial number of cases where a latent period occurs. Diagnostic procedures are not very helpful so we go ahead and operate. Sonography has not been of particular help. The only case in which it helped was one where the sonographer was able to demonstrate an ovary on the side of torsion. Therefore, it was a torsion of a parovarian cyst.

Elevated static pressure and pregnancy well-being

R. C. Goodlin, M.D., R. E. Woods, M.D., M. E. McKinney, Ph.D., P. J. Hofschire, M.D., and G. A. Russell-Churchill, R.N.
Omaha, Nebraska

Static pressure is defined as the pressure existing at all points in the circulation when the heart is stopped and is a determinant of cardiac output and blood pressure. By using the proposed relationship that static pressure = cardiac output × "resistance to venous return," estimates were made of peripheral static pressure in pregnant women. Measurements of cardiac output and venous resistance were accomplished with indirect plethysmographic techniques. Approximately 65% of pregnant women with complications had elevated values for their estimated peripheral static pressure. It is proposed that estimation of peripheral static pressure has both diagnostic and therapeutic applications in women with complications of pregnancy. (AM J OBSTET GYNECOL 1985;152:462-6.)

Key words: Pregnancy, peripheral static pressure

Approximately 75% of an animal's blood volume is contained within its venous system. In 1894, Bayliss and Starling[1] proposed that venous reactivity was an important determinant of overall cardiovascular activity. According to these investigators, Weber, in 1859, was the first to describe the concept of "static pressure," which is the pressure existing at all points in the circulation when the heart is stopped, with its values indicating how tightly the cardiovascular system is filled with blood. While we have demonstrated that many complications of pregnancy are associated with relative maternal hypovolemia,[2] it is the ratio of blood volume to the holding capacity of the circulation that is important and not the actual blood volume value. The static pressure reflects this ratio, is a determinant of cardiac output and is elevated in experimental hypertension and patients dying of heart failure.[3] Static pressure is increased in normal pregnant dogs and rabbits, presumably because of their elevated blood volumes.[4]

Guyton[3] has demonstrated that the static pressure/"resistance to venous return" is relative to cardiac output (cardiac output = static pressure/resistance to venous return). In this paper, we have used noninvasive plethysmographic techniques to estimate maternal cardiac output and relative venous resistance to return, providing estimates of "peripheral static pressure" in otherwise undisturbed pregnant women (static pressure equals cardiac output × resistance to venous return). While abnormalities of plasma volume and/or static pressure may be secondary to other phenomena, it still seems worthwhile to test the hypothesis that abnormal peripheral static pressure readings are indicative of pregnancy complications and that the values have both diagnostic and therapeutic implications.

Material

Pregnant women registered in the University of Nebraska Prenatal Clinic or those transferred to the University Hospital without evidence of venous disease were requested to participate in the study. No subjects were studied who had painful uterine contractions or were receiving drugs other than terbutaline, ritodrine, or betamethasone for treatment of premature labor or magnesium sulfate for preeclampsia.

Methods

Impedance cardiography for cardiac output was performed according to the technique described by Kubicek et al.,[5] with the IFM/Minnesota impedance cardiograph and the Surcon impedance cardiogram microcomputer, Model 7000. The cardiac index was calculated while the subject was apneic, with five to 10 determinations made and runs accepted with a range of $<10\%$.[5] The venous capacitance was performed with a Stim Tech impedance phlebograph according to the technique of Tripolitis et al.[6] and the venous resistance was estimated from the slope of the venous outflow of a recording of the impedance phlebogram (Fig. 1). Efforts were made to achieve relaxation in the subject and to properly position the subject in the left lateral position with the extremity elevated. However, if, despite these efforts, the venous resistance values suggested overt venous obstruction, the subject's data were excluded. The abnormal values were considered to reflect uterine pressure or the failure of the subject to relax. The highest values obtained for venous capacitance

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were used and the lowest value for venous resistance, or the R ratio (Fig. 1) of the length of the base of the triangle to its height, was recorded. The coefficient of variation of the venous capacitance in the same subjects on succeeding days was ±23%, the venous resistance was ±10%, and the cardiac index was ±18%. Plasma volume was determined with the Evans blue technique as previously described, and its value was corrected by 0.9 to conform with our iodine 125–labeled human serum albumin technique.[2]

Except for the plasma volume determination with Evans blue, the techniques were noninvasive. After informed oral consent had been obtained according to the rules of the Institutional Review Board, the double-banded electrodes of the impedance phlebographs were applied to the neck and at the level of the xyphoid for determining cardiac output and then to the left calf for measurements of venous reactivity. The static pressure estimation was calculated by the cardiac index × the estimate of venous resistance (R angle) × 36. This constant was used in order to have normal peripheral static pressure be approximately 10, since the literature suggests that the average static pressure for the anesthetized, pregnant animal is between 9 and 10 torr.[4]

Results

Combined studies have shown that excessive values for resistance to venous return were obtained in 48% of women in labor and in 5% after the thirty-sixth week of pregnancy.[7] Table I lists the impedance phlebographic values for normal pregnant women and those with complications. The normal upper range of segmental static pressure was considered to be "20" (mean + 3.5 SD). For purposes of discussion, only those subjects with complications who had abnormal peripheral static pressure values are listed. There were five subjects in premature labor, four with mild preeclampsia, and four with fetal growth retardation who had estimates of static pressures that were <"20" and therefore are not included in the table.

Twelve subjects with cardiac outputs >6 L/min had venous resistance values less than 0.07, while only eight of 53 with lower cardiac outputs had such low values ($p < 0.01$).

Comment

We have suggested that the measurement of maternal venous reactivity is able to select the majority of women with abnormal pregnancies.[7] The added advantage of considering the concept of static pressure is its implication in the reflection of overall venous vascular function to plasma volume alterations. Resistance to venous return, according to Guyton et al.,[8] constitutes only 10% of the total peripheral resistance. While an increase in arterial resistance will cause a proportional increase in arterial pressure, an increase in resistance to venous return has the opposite effect of causing a decrease in arterial pressure. This is because changes in arterial resistance have much less effect on cardiac output than do equal changes in resistance to venous return. On the other hand, a decrease in resistance to venous return causes a marked increase in cardiac output, which can secondarily cause hypertension because arterial pressure = cardiac output × arterial resistance. For these reasons, if both the arterial resistance and resistance to venous return increase simultaneously, there is likely to be little or no change in arterial pressure even though the total peripheral resistance has increased markedly. If the total peripheral resistance is relatively constant, blood pressure will then vary with static pressure.

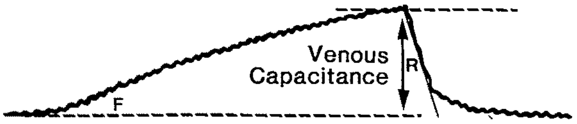

Fig. 1. Schematic impedance phlebogram recording demonstrating increase in calf blood volume after tourniquet occludes vein and decrease of calf blood volume with release of tourniquet. *R,* Relative venous resistance; *F,* relative arterial flow.

The plethysmographic techniques are noninvasive and well tolerated by pregnant women. Table I lists the results of our applications of these techniques. Since estimates of peripheral static pressure in some cases of pregnancy complications are in excess when compared with values of static pressure in anesthetized laboratory animals, our simplified concepts may require modification. While the technique is simple, the concept of resistance to venous return and its relationship to cardiac output in the intact animal is controversial. Furthermore, our technique for measuring resistance to venous return is unconventional and its units of measurement are arbitrary. The technique and its results are presented despite these caveats because of the possibility of establishing a more precise relationship between alterations of venous function, plasma volume, and pregnancy complications.

In our studies, those pregnant women with the highest cardiac outputs were those who had the lowest values of venous resistance, which is consistent with the assumption that static pressure is relatively constant and that cardiac output varies inversely with resistance to venous return (cardiac output equals static pressure/resistance to venous return). These concepts of static pressure may also explain some of the cardiovascular findings in pregnancy. For instance, in 1917, Bolton[9] showed that increased static pressure is often due to increased blood volume. Pregnant women have an in-

Table I. Cases of elevated static pressure (impedance plethysmographic estimation)

Case No.	*Diagnosis**	*No.*	*Plasma volume (ml/kg)*	*Cardiac index†*	*Resistance to venous return‡*	*Static pressure§*
–	Normal (24-36 wk)	50	68 ± 6	3.1 ± 0.5	0.09 ± 0.02	"10" ± 3.5
1A	Premature labor	11	46 ± 8	2.7 ± 0.7	0.31 ± 0.08	"30" ± 9
1B	With terbutaline	7	58 ± 11	5.8 ± 1.3	0.11 ± 0.05	"23"
2A	Preeclampsia	8	38 ± 12	4.8 ± 1.7	0.28 ± 0.11	"48" ± 17
2B	With magnesium sulfate	4	49	5.9	0.19	"40"
3	Fetal growth retardation	6	41 ± 7	3.2 ± 1.0	0.38 ± 0.07	"46" ± 11

Values are mean ± SD.

*Some with multiple diagnoses.

†Cardiac index = cardiac output/surface area.

‡R angle, Fig. 1.

§Static pressure = cardiac index × resistance to venous return.

crease in both blood volume and static pressure above the nonpregnant values,[4] which may explain their propensity to develop hypertension.[3] With their increased static pressure and normal resistance to venous return, the increased cardiac output found in pregnant women is to be expected. Women with preeclampsia have, by our findings, even higher values of peripheral static pressure, perhaps related to the failure of plasma volume expansion, requiring increased venous tone and/or the failure of the venous capacitance system to increase.

In normal pregnancy, trophoblasts invade the media of the myometrial cells of the placental bed in early pregnancy, with the endovascular invasion reaching the final stages in the spiral arteries by the eighteenth week. Brosens et al.,[10] as well as others, have shown that this trophoblastic invasion and replacement of the media provide for dilatation of the spiral arteries, forming an arteriovenous fistula and significantly changing the volume and characteristics of the uterine blood flow. When these anatomic and physiologic changes of the placental bed fail to develop, there is fetal growth retardation, sometimes in association with preeclampsia.[10] Decreased maternal plasma volume expansion and increased venous tone are associated with this same clinical subset of fetal growth retardation and preeclampsia, and since arteriovenous fistulas are associated with hypervolemia, the increase in plasma volume during normal pregnancy is probably secondary to this fistula formation that occurs in the placental bed.[2,7] These concepts suggest that while a therapeutic impact may not be made on the degree of placental bed infusion, it nevertheless may be possible to modify the maternal effects of hypoperfusion such as in preeclampsia with an appropriate understanding of the compensatory maternal venous mechanism.

Understandably, there have been no direct estimates of static pressure in living humans. However, it appears possible with noninvasive plethysmographic techniques to indirectly determine levels of peripheral static pressure in pregnant women. Concerns about the technique of peripheral static pressure estimations include the fact that the venous resistance value is a peripheral estimate and instead should be a central measurement or include many peripheral measurements. Our previous experience of combining arm with leg venous reactivity measurements was not satisfactory.[7] In addition, the lower limb venous drainage is in common with the uterine venous drainage, suggesting that leg studies are a more reliable indicator of significant venous changes during pregnancy. Another concern is the validity of the concept of the clinical estimate of resistance to venous return. According to Guyton et al.,[3,8] this includes all venous and some arterial resistance, but we have focused on the venous factor because the resistance to venous return increase is approximately 25 times as much for a given increase in venous resistance as for a similar increase in arterial resistance. In addition, changes in limb volume in response to congestion (cuff) pressure or the height of the impedance phlebogram recording (venous capacitance of Fig. 1) represent a complex interplay of many factors. These include cardiac output, local arterial flow, local arterial spasm, the preinflation venous pressure, the slope of the venous pressure volume curve, and the elastic characteristics of the venous wall as well as the venous muscular system. Alexander[11] showed that the dilated veins have less distensibility, apparently because the fibrous elements of the venous wall adventitia were involved. Estimates of venous return from the characteristics of the outflow curve of the phlebogram recording are likewise complex. The outflow depends not only on the amount of upstream venous obstruction, such as the pregnant uterus, but also on the dilatation and elastic properties of the vein and degree of venous tone. We have assumed that the abnormal venous resistance values suggesting thrombosis found in the majority of women in labor or in 5% of those in late pregnancy reflect, instead, venous obstruction by the pregnant uterus or excessive catecholamine levels or the inability of the women to relax.[7]

There are also disagreements over the acceptance of impedance cardiac plethysmographic techniques during pregnancy.[12-14] Changes associated with pregnancy could produce alterations in skin electrical conductivity or shifts of the diaphragm, and changes in diameter of the thorax could modify the conventional relationship between blood volume and alterations in chest impedance, all altering apparent cardiac output values. Nevertheless, some studies have obtained excellent correlation during pregnancy between the cardiac output as measured with the impedance cardiographic technique and those with the Swan-Ganz thermodilution method.[13, 14] In contrast to findings from traditional techniques, cardiac outputs with the impedance techniques have been described as maximum at 18 to 24 weeks of pregnancy. Women with severe preeclampsia have been found to have either a low or decreased cardiac output.[12, 13] These differences with the noninvasive impedance technique may reflect the more basal condition of the subjects.[14]

Other studies of venous reactivity during pregnancy have described increases in venous distensibility and venous capacitance and venous reactivity alteration during preeclampsia.[15] Hunyor et al.[16] proposed that the abnormal venous reactivity observed in pregnant women represented the increase in plasma volume and the subsequent distended veins. These Australian investigators regarded pregnancy as a potentially hypertensive state because of these women's abnormal venous reactivity.

The clinical application of estimated static pressure in pregnant women would be used to identify potentially high-risk pregnant women as well as to suggest specific therapy. Furosemide, nitroglycerine, and amyl nitrite are drugs that increase venous capacitance.[17] Information is not available as to whether these drugs selectively affect resistance to venous return or total venous reactivity. In a limited study, we have used these drugs with apparently good results in combination with plasma volume expansion in pregnant women with complications who also had elevated static pressure.

In this study, not all women with abnormal pregnancies had abnormal peripheral static pressures, indicating either that our techniques were imprecise or that abnormal cases represented a heterogeneous group in terms of venous reactivity and static pressure values. While these techniques and findings are encouraging, they are not considered definitive.

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Discussion

Dr. Thomas Kirschbaum, Bethesda, Maryland. I think Dr. Goodlin is one of the most ingenious, farsighted people concerned with investigation in this area. I will skip any reference to the difficulties in measuring blood pressure in Omaha; I just do not understand that at all. Also, I would like to point out that not all of Dr. Goodlin's ideas have worked out well. We were residents together and one day he exteriorized the stomach in order to do a colostomy. This idea has never been pursued by other physicians. The fundamental message was relatively clear—that it is meaningless to be concerned with blood volume unless you know the size of vascular space even though we make use of that omission all the time, and the venous tone is a major determinant of vascular space and size of the vascular space. I think Dr. Goodlin is exactly right in those two observations. The third set of observations is important for people to explore who are concerned with maternal-fetal physiology. He has picked a series of measurements that are, at least currently, impossible to make and has done the best he can with them. We need to stimulate other people to follow the fundamental precepts he has laid down. The recent static pressure was, as you could see from his presentation, a hypothetical one derived from a simple "doughnut" view of the circulatory system. When Starling, with his series of collaborators, began exploring the mechanics of the heart by changing the venous return rates and changing the size of the ventricle during diastole, he had a system in which he could stop the dog's heart and stop the pump and measure the height of blood in the reservoir and the circulatory pressure, the mean circulatory pressure, which is what is probably more commonly used than the term static pressure. I think it fair to say that it will never be possible to make this measurement in a human. It may, however, have some theoretical usefulness. Whenever there is a pressure, it can be derived by multiplying a flow value times a resistance, if the fact is ignored that circulation is not a DC analogue system. There is not constancy in flow but flow in pressure and resistance are pulsatile events that change in time. That is a major assumption to throw into the pot.

There are some others that are embedded in the techniques that Dr. Goodlin has used. The flow measurement is derived from impedance measurements and the thorax during the cardiac cycle. If an alternating current is run into the chest and the potential that evolves is measured, you can calculate the impedance; if you plot the impedance as a function of time, you can calculate the derivative of the impedance, in animals at least. It correlates with the output of blood through the aorta. Whether it does in a human has never been entirely clear. As Dr. Goodlin points out quite clearly, whether pregnancy changes the impedance of the chest and of the heart by virtue of elevation of the diaphragm and changing the contour of the chest has not been determined either. These are uncertainties that rest in the flow measurement. The resistance measurement has some assumptions in it as well. You remember from Dr. Goodlin's diagram that the R angle must be assumed to be derived from the egress of venous blood which is trapped in the extremity during the time the cuff was applied. There are two problems with that. One is that, as the cuff is applied, pressure builds up until continued arterial inflow is met by hydrostatic pressure below which stops arterial inflow. So one of the components of the volume increment is arterial blood. The second problem is transudation, since lymph formation fills the occluded extremity as well. That upward slope will go on almost indefinitely if the cuff is kept on even though the pressure below the cuff has exceeded venous pressure. That means that when the R angle is measured and when the resistance of the egress is measured, the value is of something more than venous blood. Probably a more serious objection in this
area has to do with the generalizati
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entire circulation because of the stril
takes place in the venous pressure
lower extremities in pregnancy. Thi
to the jetlike return of uterine vein
rate of 1 L/min in late pregnancy,
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assume that the resistance outflow
pregnancy represents the whole circ
worry about whether the patient is
down at the time blood pressure is
mean by any of these things to detr
lin's fundamental thesis, which is th
tant area in which to do investiga
currently stuck at the point where a
does not suffice.

Dr. Goodlin (Closing). I apprec
of Dr. Kirschbaum, as he is an exc
As he stated, the main purpose of
attempt to evaluate the venous reac
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sure plasma volumes during pregn
late on their significance.

We have turned to the venous sic
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estimates of static pressure. The tecl
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have the same etiology or mechanis
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article, the significance of elevated st
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occasional article on the subject sinc
not been an era of active investigatio
with normal pregnancies have elevat
that it is logical that venous reactivit
be studied intensively in an effort to
treat cases of pregnancy complicati

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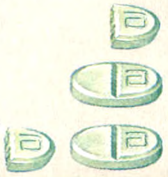

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WARNING:

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. OGEN SHOULD NOT BE USED DURING PREGNANCY.

According to some investigators, the use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. Studies have reported that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] In one of these studies, this risk was estimated as not greater than 4 per 1000 exposures.[7] Furthermore, there are reports that a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these reported changes are histologically benign, the investigators have not determined whether they are precursors of adenocarcinoma.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies in the offspring, including heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. OGEN has not been studied for these uses, and therefore should not be used during pregnancy. There is no evidence from well controlled studies that progestogens are effective for these uses.

If OGEN (estropipate tablets) is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the question of continuation of the pregnancy should be addressed.

INDICATIONS

OGEN (estropipate tablets) is indicated for the treatment of estrogen deficiency associated with:

1. Moderate to severe *vasomotor* symptoms of menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.

OGEN (ESTROPIPATE TABLETS) HAS NOT BEEN TESTED FOR EFFICACY FOR ANY PURPOSE DURING PREGNANCY. SINCE ITS EFFECT UPON THE FETUS IS UNKNOWN, IT CANNOT BE RECOMMENDED FOR ANY CONDITION DURING PREGNANCY (SEE BOXED WARNING).

CONTRAINDICATIONS

OGEN should not be used in women with any of the following conditions:

1. Known or suspected cancer of the breast.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (See Boxed Warning).
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use.

WARNINGS

1. *Induction of malignant neoplasms.* Long-term continuous administration of natural and synthetic estrogens in certain animal species has been reported by some investigators to increase the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning).

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent long-term followup of a single physician's practice has raised this possibility.[18] Therefore, caution should be exercised when administering estrogens to women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. Careful breast examinations should be performed periodically.

2. *Gall bladder disease.* A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens,[17] similar to the 2-fold increase previously noted in users of oral contraceptives.[19,22] In the case of oral contraceptives, the increased risk appeared after two years of use.[22]

3. *Effects similar to those caused by estrogen-progestogen oral contraceptives.* There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat postpartum breast engorgement would be more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in women receiving estrogens for postpartum breast engorgement.[20,21]

a. *Thromboembolic disease.* It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[22-29] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.[30,31] An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives.[32,33] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism; it should also be discontinued during periods of prolonged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found[17,34] this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk. Therefore estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

b. *Hepatic adenoma.* Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[36-38] Although benign, and rare, these may rupture and cause death through intraabdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[37] The relationship of this malignancy to these drugs is not known at this time.

c. *Elevated blood pressure.* Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with use of estrogens in the menopause[39] and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. *Glucose tolerance.* A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

4. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS

A. General Precautions.

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

2. Fluid retention — Estrogens may cause some degree of fluid retention. Therefore, patients with conditions such as epilepsy, migraine, and cardiac or renal dysfunction, which might be influenced by this factor, require careful observation.

3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression.[22] Although it is not clear whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size during estrogen use.

6. The pathologist should be advised of the patient's use of estrogen therapy when relevant specimens are submitted.

7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen.

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

B. Information for the Patient. See text of Patient Package Insert which appears after PHYSICIAN REFERENCES.

C. OGEN (estropipate tablets) cannott be recommended for use during pregnancy. See Contraindications and Boxed Warning.

D. Nursing Mothers. Estrogens have been reported to be excreted in human breast milk.

ADVERSE REACTIONS

(See Warnings regarding reports of possible induction of neoplasia, unknown effects upon the fetus, increased incidence of gall bladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

1. *Genitourinary system.*
Breakthrough bleeding, spotting, change in menstrual flow.
Dysmenorrhea.
Premenstrual-like syndrome.
Amenorrhea during and after treatment.
Increase in size of uterine fibromyomata.
Vaginal candidiasis.
Change in cervical eversion and in degree of cervical secretion.
Cystitis-like syndrome.

2. *Breast.*
Tenderness, enlargement, secretion.

3. *Gastrointestinal.*
Nausea, vomiting.
Abdominal cramps, bloating.
Cholestatic jaundice.

4. *Skin.*
Chloasma or melasma which may persist when drug is discontinued.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Loss of scalp hair.
Hirsutism.

5. *Eyes.*
Steepening of corneal curvature.
Intolerance to contact lenses.

6. *CNS.*
Headache, migraine, dizziness.
Mental depression.
Chorea.

7. *Miscellaneous.*
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria.
Edema.
Changes in libido.

ACUTE OVERDOSAGE

Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that serious ill effects do not occur. Overdosage of estrogen may cause nausea and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

1. *Given cyclically for short-term use:*

For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., 3 weeks on and 1 week off).

Attempts to discontinue or taper medication should be made at 3 to 6 month intervals.

The usual dosage range is one OGEN .625 (estropipate) Tablet to one OGEN 5 Tablet per day.

2. *Given cyclically:*

Female hypogonadism. Female castration. Primary ovarian failure. The lowest dose that will control symptoms should be chosen. A daily dose of one OGEN 1.25 Tablet to three OGEN 2.5 Tablets may be given for the first three weeks of a theoretical cycle, followed by a rest period of eight to ten days. The same schedule is repeated if bleeding does not occur by the end of the rest period. The duration of cyclic estrogen therapy necessary to produce withdrawal bleeding will vary according to the responsiveness of the endometrium. If satisfactory withdrawal bleeding does not occur, an oral progestogen may be given in addition to estrogen during the third week of the cycle.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

OGEN (estropipate tablets, USP) is supplied as OGEN .625 (0.75 mg estropipate), yellow tablets, **NDC** 0074-3943-04; OGEN 1.25 (1.5 mg estropipate), peach-colored tablets, **NDC** 0074-3946-04; OGEN 2.5 (3 mg estropipate), blue tablets, **NDC** 0074-3951-04; and OGEN 5 (6 mg estropipate), light green tablets, **NDC** 0074-3958-13. Tablets of all four dosage levels are standardized to provide uniform estrone activity and are grooved (Divide-Tab®) to provide dosage flexibility. All tablet sizes of OGEN are available in bottles of 100.

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Bimonthly. Institutions: $69.00; Individuals: $34.00; Students, residents: $25.00. Official publication of the American Society for Surgery of the Hand.

THE JOURNAL OF LABORATORY AND CLINICAL MEDICINE
Monthly. Institutions: $91.00; Individuals: $56.00; Students, residents: $38.40. Official publication of the Central Society for Clinical Research.

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AJS-044

The age extremes for reproduction: Current implications for policy change

Ezra C. Davidson, Jr., M.D., and Teiichiro Fukushima, M.D.
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The changing demographic features of births in the United States include an increasing number of older women and a decreasing number of adolescents giving birth. Births in adolescents have lower risks than those in women more than 34 years of age and probably of those more than 30 years of age. There is an increase in complicated pregnancies in the United States, related, no doubt in part, to the above. Older women require more costly, high-technology prenatal care, such as genetic counseling, genetic antenatal diagnosis, amniocentesis, ultrasonography, and electronic fetal heart rate testing. The financing of health care needs to recognize these changes. Detailed studies of the economics of perinatal care, more specific to patient population mix and complication-treatment patterns are needed to establish priorities with the payment system to assure appropriate care. (Am J Obstet Gynecol 1985;152:467-73.)

Key words: Pregnancy, prenatal care services, adolescent pregnancy, age extremes and pregnancy, pregnancy risks

In this country increasing attention is being focused on reducing the cost of health care and the rate of increase in cost. Powerful tools are being implemented to increase competition within the health care system and control or project cost.

The most recent national governmental program is diagnosis related groups. However, other plans have entered the system with varying levels of government, private insurance, and corporate support: second surgical opinions, health maintenance organizations, prepaid health plans, various physician-provider groups, and contracts with selective hospitals for purposes of reducing costs.

In addition, there has been a recent pattern of reduction of public funding for maternal health programs on both the local and national levels.[1] Federal funding cuts have affected the services to pregnant women in three major areas: medicaid, Title V Maternal and Child Health Block Grants, and the community health centers and preventive health services programs.[1] Medicaid reaches approximately 3.2 million women of childbearing age, and under the Omnibus Reconciliation Act of 1981, Congress approved a 4 billion dollar cut for fiscal years 1982 through 1985. The Maternal and Child Health Block Grant appropriation in fiscal year 1982 of $373 million was 18% less than in fiscal year 1981. In fiscal year 1982 community health centers were cut by 13%.

Private third-party funding is being reduced as with the Blue Shield Preferred Provider plans in California where physicians and hospitals are under cost-control contracts.

With these current forces at play on the economics of health care, we at the King/Drew Medical Center, a public hospital in Los Angeles, were forced to reexamine our programs for perinatal services and compare them to what were the unmet needs. On analysis of our data and review of other local and national data, we believe that this experience can be extrapolated to project a national and more general prospective. This report emphasizes the need for further and more detailed economic and perinatal health care studies.

Patterns of clinical care in obstetrics are changing to those which are clearly more costly than the former ones. Most notably this involves genetic counseling and antenatal genetic diagnosis, electronic fetal monitoring for both antenatal and intrapartum fetal assessment, the use of ultrasonography in obstetrics, amniocentesis, increase in cesarean sections, and the care and treatment of the neonate.[2,3] The pro and con arguments concerning these modalities will not be engaged in here, but the most conservative of critics of their use would agree that all have a role to play in contemporary obstetrics beyond their use in earlier times. The increased cost of certain elements of perinatal care is a fact.

In concert with these changing economic forces and the changing patterns of perinatal care is a changing profile of the American woman requiring perinatal services.[4,5] The total number of births is beginning to in-

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Table I. King-Drew Medical Center perinatal statistics, July, 1983, to June, 1984

*Weight** *(gm)*	*Births* *(n)*	*Stillbirths* *(n)*	*Neonatal deaths* *(n)*	*Perinatal mortality rate†*
≥2500	5433	10	3	2.4
<2500 ≥1500	366	10	8	49.2
<1500	89	14	26	449.4
Total	5896	35	37	12.2

Perinatal mortality rate is number of deaths per 1000 births, weight ≥500 gm, gestationsl age ≥20 weeks.
*Weights missing, eight; < 500 gm, 3; malformations, 10.
†Uncorrected; corrected rate, 11/1000.

Table II. King-Drew Medical Center perinatal statistics, July, 1983, to June, 1984—Prenatal care at hospital

*Weight** *(gm)*	*Births* *(n)*	*Stillbirths* *(n)*	*Neonatal deaths* *(n)*	*Perinatal mortality rate†*
≥2500	1156	3	1	3.4
<2500 ≥1500	76	2	4	92.1
<1500	11		3	272.7
Total	1244	5	8	10.5

Perinatal mortality rate is number of deaths per 1000 births, weight ≥500 gm, gestational age ≥20 weeks.
*Weights missing, one; <500 gm, zero; malformations, two.
†Uncorrected; corrected rate, 10/1000.

crease and the age distribution is shifting to a lower number of adolescents and a higher number of women over 30. These changes, increased births and higher-aged pregnant women, imply increased costs.

The converging shifts in current economic policies, more technological and costly patterns of perinatal care, and the demographic changes of the pregnant woman define a dilemma that needs to be more clearly understood and articulated to avoid substandard care and possible injury from inadequate care.

Material and methods

Three major sources of data were used for this study. First, data for the fiscal year July, 1983, through June, 1984, from the perinatal services at the King/Drew Medical Center in the south area of Los Angeles County, California, initially directed our attention to review the other two available sources of data: The County of Los Angeles Department of Health Services data[5-7] and the annual vital statistics summaries from the National Center for Health Statistics,[4] including the yet unpublished data from the National Natality Survey from the National Center of Health Statistics, United States Public Health Service, Department of Health and Human Services (Samuel Kessel, M.D., personal communication, 1984).

The King/Drew data consisted of 5896 births at the medical center. These data were characterized in terms of the overall perinatal mortality rates* according to (1) birth weight distribution, (2) source of prenatal care (King/Drew, our 12 divisions of the ambulatory south area of the Los Angeles County Health Department Clinic network and (3) no prenatal care, or care received outside this King/Drew network).

The births were 85% Hispanic and 13% black. This patient-population mix has not changed in the last 6 years. There were 272 patients under 17 years of age and 512 patients over 34 years of age.

The latest available perinatal data were used from Los Angeles County prepared in 1984: *A Report on Selected Health Status Indicators*[5, 6] and *Vital Statistics Reports, 1976-1982*,[7] all compiled by the Data Collection and Analysis Division, Public Health Programs, County of Los Angeles Department of Health Services.[5-7] These data are reported according to age, birth weight, ethnic group, and geographic area within the county.

The unpublished United States data are from the 1972 and 1980 National Natality Surveys, both based on certificates of live births sampled from the United States vital registration system and expanded by mail follow-up of mothers, hospitals, and physicians associated with those births (Samuel Kessel, M.D., personal communication, 1984). These data were collected by

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*Computed as fetal deaths beyond 20 weeks or 500 gm, plus neonatal deaths to 28 days per 1000 births.

Table III. King-Drew Medical Center perinatal statistics July, 1983, to June, 1984—no prenatal care

*Weight** *(gm)*	*Births* *(n)*	*Stillbirths* *(n)*	*Neonatal deaths* *(n)*	*Perinatal mortality rate†*
≥2500	679	2	1	4.4
<2500 ≥1500	74	1	1	27.6
<1500	31	7	9	516.1
Total	787	11	11	28.0

Perinatal mortality rate is number of deaths per 1000 births, gestational age ≥20 weeks.
*Weights missing, three; <500 gm, one; malformations, two.
†Uncorrected; corrected rate, 27/1000.

Table IV. King-Drew Medical Center perinatal statistics, July, 1983, to June, 1984—prenatal care, south area

*Weight** *(gm)*	*Births* *(n)*	*Stillbirths* *(n)*	*Neonatal deaths* *(n)*	*Perinatal mortality rate†*
≥2500	2486	2	0	1.2
<2500 ≥1500	102	5	2	68.4
<1500	12	1	6	583.3
Total	2602	8	8	6.1

Perinatal mortality rate is number of deaths per 1000 births, weight ≥500 gm, gestational age ≥20 weeks.
*Weights missing, two; <500 gm, zero; malformations, one.
†Uncorrected; corrected rate, 6/1000.

Table V. King-Drew Medical Center births

Maternal age *(yr)*	*No. of births*	*Low–birth weight infants* *(%)*	*Perinatal mortality rate*	*Cesarean sections* *(%)*
<17	272	8.0	7	8.1
≥34	516	8.3	17	22.9
All ages	5896	7.6	12	13.9

the National Center for Health Statistics, United States Public Health Service, Department of Health and Human Services. The National Center for Health Statistics conducted the surveys to expand the information reportable through the vital registration system, to provide maternal estimates of characteristics not available through the vital registration system, and to permit trend studies with follow-up survey data collected in previous years. In the 1972 and 1980 National Natality Surveys, questionnaires mailed to hospitals where births occurred included checklists of specific underlying medical conditions of the mother, complications of pregnancy, and complications of labor. The births were a stratified, weighted sample of more than 10,000 births in order to make National estimates.

Results

The King/Drew data show differences in perinatal mortality rates of patients who received care within the network (hospital clinics and the 12 south area ambulatory clinics managed by the medical center) as compared to those patients who did not receive prenatal care: 7.5 versus 28 deaths per 1000 births (Tables I to IV). The perinatal mortality rates value of 10 for patients who were seen at the Medical Center no doubt reflects the higher risk of this referred group as compared to the value of 6 for patients seen in our south area clinics.

The adolescent patients less than 17 years of age, in whom the greater risk would be expected, had a low perinatal mortality rate value of 7.

The cesarean section rate was 8.1% in this adolescent group. The rate of low–birth-weight infants was 8% (Table V), which was not significantly different from the overall King/Drew rate of 7.6%. The rate of low–birth-weight infants in Los Angeles County for women under age 20 was 8% in 1982, the latest available data, 6% for women 20 to 34, and 7.4% for women 35 and

Table VI. Los Angeles County births by maternal age 1976 and 1982

Maternal age (yr)	*1976*	*1982*
<15	351 (0.3)*	338 (0.2)
15-19	18,888 (16.3)	17,824 (12.8)
30-34	16,505 (14.2)	24,959 (18.0)
35-39	5516 (4.7)	8716 (6.2)
Total	115,590	139,241

*Percentage of total births.

Table VII. Trends in births to teenage mothers* in the United States

Maternal age (yr)	*1960*	*1979*	*1981*
<15	6780	11752	9632
15-17	173,507	223,590	187,397
18-19	413,459	421,118	339,995
Total	593,746	656,456	537,024

*From National Center for Health Statistics, annual volumes.

Table VIII. Los Angeles County births

	1979	*1980*	*1981*	*1982*
No.	123,292	131,111	136,219	138,888
Low–birth weight	6.3	6.2	6.3	6.2
Perinatal mortality rate	17.6	16.2	15.9	NA

NA = Data not available.

Table IX. National Natality Surveys—Trends in maternal complications

	1972 (%)	*1980 (%)*
One or more underlying medical conditions	13.9	19.0
One or more complications of pregnancy	16.3	27.8
One or more complications of labor	20.2	28.3

*Samual Kessel, M.D., personal communication, 1984.

over. This would suggest some increased risk in both the youngest and oldest ages.

The over-34 group who were delivered at King/Drew had a significantly higher cesarean section rate of 22.9%, two thirds of which were primary. The rate of low–birth-weight infants was 8.3% and the perinatal mortality rate value was 17 (Table V). These data rather sharply contrast with the figures for adolescents where the cesarean section rate was 8.1%, the rate of low–birth-weight infants was 8%, and perinatal mortality rate value was 7.

The births in Los Angeles County have been on the rise in recent years, as are national births, and show an increasing trend in maternal ages over 30 and a decreasing number of births in ages under 20 (Tables VI to VIII). In Los Angeles County the percentage of births to women under 20 years of age dropped from 16.6 in 1976 to 13 in 1982; on the other hand, births to women over 30 years of age increased from 18.9% to 24.2%. Similar trends occurred nationally: Births to women under 20 years of age have decreased by 18% since 1979 (656,456 births) to 1981 (537,024). The total number of women in the childbearing age group, 15 to 44 years, is projected to increase by 8% from 1979 to 1985. The largest increases will occur among women from 30 to 34 (16.3%) and 35 to 39 (26.7%).[8]

The National Natality surveys for 1972 and 1980 show an increasing percentage of women with medical complications associated with pregnancy and an increase in antepartum and intrapartum complications (Table IX).

Comment

These seemingly disparate data are presented here to describe a local problem carried to a national perspective. There are unmet perinatal health care needs and changing patterns of care that will require a relative increase in the most costly, high-technology care. This is despite the forces at play to reduce costs.

It appears from the King-Drew data that prenatal care will improve the perinatal mortality rate, as has been shown by others. Although these data do not specifically quantitate the differences, only the adolescents had pregnancy-induced hypertension as a complication to a greater extent than women over 34 years of age. Size-dates discrepancy required sorting out perhaps about equally in both groups. However, the older women required more complex care and surveillance than the youngest ones, as seen by the indirect evidence of higher perinatal mortality rates, higher percentage of low–birth-weight infants, and cesarean section rates. One of the more obvious suggestions from the National Natality Survey data is that increasing maternal age may be a major contributor to the increasing number of complications in pregnancy. Age alone is the largest single indication for genetic counseling and diagnosis both in our population (over 90%) and nationally.[9] This technology alone being provided more thoroughly on a national basis will be a significant cost to the system.

There has been, in recent years, an increasing focus on the needs of the pregnant adolescent. This is appropriate, for these pregnancies raise many unresolved social, economic, and family structure concerns. However, the earlier presumption that because of their young age their medical problems were more serious does not now appear to be supported by available data. If resources are available to provide routine prenatal care, their pregnancy outcomes should be similar to those of women in their peak reproductive years.

What has been less emphasized are the increasing number of women over 30 who are giving birth and, with the changing patterns in perinatal practices, the increases in total services and costs that will be required when these are coupled with the increased medical care needs.

A quick scan of the current literature in obstetrics and discussion with perinatologists suggest a shift toward more expensive ultrasound and electronic fetal heart rate testing in the evaluation of the fetus rather than use of less costly biochemical and hormonal assays, for instance, estriol levels. Naeye[10] concluded from his study of 44,386 pregnancies that advancing maternal age influences frequency and outcome of antenatal disorders. He noted an increasing perinatal mortality rate value from 25 at ages 17 to 19 to 69 at age 39. Stillbirths accounted for 92% of the increase, with one half associated with disorders of uteroplacental underperfusion. This would require more antenatal fetal and maternal testing for proper surveillance of these pregnancies. This information supports advancing maternal age as an explanation for the National Natality Survey data of increased complications from 1972 to 1980.

The adolescent is generally a low-risk patient for perinatal mortality and low–birth-weight infants, from our data and those of others.[11, 12] This does not ignore the large social and economic risks of the adolescent population, who require support and social and educational services,[13] but the medical model may need to shift its resources to services that will directly reduce health risks in other areas and encourage these social science and education disciplines to meet the nonmedical needs.

Older women require more costly, high-technology prenatal care, such as genetic counseling, antenatal genetic diagnosis, amniocentesis, ultrasonography, and electronic fetal heart rate testing. Detailed studies of the economics of perinatal care, more specific to patient-population mix and complication-treatment patterns, are needed to establish priorities with the payment system to assure appropriate care.

Individual and institutional practices will have to reflect the changing perinatal care demands and to argue with third-party payers of all types the need to provide adequate compensation to provide these services.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. ROBERT A. SACK, Whittier, California. Dr. Davidson's paper raises the question of the need for policy change regarding the increasing number of older maternity patients. He has documented their number to be increasing as the number of teenage pregnancies is decreasing. His statement that older women require more costly, high-technology prenatal care is an economic fact of life. His recommendation that detailed studies of the economics of obstetric care be carried out is one of high priority.

This study, from a public hospital, showing more than double the perinatal mortality and almost three times the cesarean section rate in the older patient is suggestive of higher risk in this group. Is the pregnant patient older than age 34, who is in good general health, any more at risk than she was at an earlier age? This is the basic unanswered question.

In order to add some data, a retrospective study of the fate of the older patient delivered in a private hospital was undertaken. The study was conducted in the Whittier, California, Presbyterian Intercommunity Medical Center from July 1, 1979, to June 30, 1984. This is a 357-bed suburban private hospital affiliated with the School of Medicine of the University of Southern California.

During this 5-year period there were 9722 deliveries and 418 (4.7%) were by women over age 34. There were 405 infants weighing >2500 gm with a zero perinatal mortality rate. Nine infants, two of which were stillborn, weighed from 1500 to 2500 gm. There were four infants weighing under 1500 gm; three were stillborn and one, an 800 gm infant, was a neonatal death. The 13 low–birth-weight infants (3.1%) with six perinatal deaths are too few to statistically evaluate. Of interest, there were seven infants in this series weighing >4500 gm. There was one Down's syndrome infant born to a woman who declined amniocentesis for religious reasons.

The lower percentage of women over 34 years of age in the private hospital series reflects the population from which they are drawn. No doubt, this population has a greater number of women who have been surgically sterilized. They also have better access to contraception and abortion.

The private hospital series revealed the percentage of low–birth-weight infants to be the same as for all ages delivered in the hospital. This probably reflects better lifelong, as well as prenatal, nutrition of the mother.

Only when cesarean sections are considered does the private series exceed a parameter documented in the public hospital study. Of the 418 deliveries in the private series, 124 were delivered by cesarean section. This is a cesarean section rate of 29.7%, as compared to a rate of 25.6% in all cases over the same 5-year period. When the 63 primiparous patients over age 34 are considered, the cesarean section rate was 61%. In multiparous patients over 34 who had not had a previous cesarean section, the rate was 12.5%.

There are several factors other than age influencing pregnancy in the older patient. Two of these can be inferred from the studies presented here. They are the iatrogenic influence and the socioeconomic influence.

The iatrogenic influence arises because in these litigious times obstetricians must "timely test" in order to avoid the charge of "failure to diagnose." These tests are expanding in number, increasingly expensive to perform, and carry a certain amount of risk for both the mother and the unborn.

This is not to say that testing is entirely inappropriate or not indicated, because the present-day obstetrician must obey ever more stringent standards to avoid a charge of malpractice. We may need a new indication for cesarean sections to go along with "failure to progress." We could add the indication "risk to the obstetrician" to our nomenclature.

However, all the blame cannot be placed on the doorstep of the legal profession. We must accept our share of blame in this matter. The root cause of the problem may be the concept of the "premium baby." All babies should be "premium babies," but the cost of treating all pregnancies as "high risk" is not practical or economically feasible.

The difference in outcome in the two series compared here is probably due to two factors. Patients in the Whittier study, in the great majority of instances, are from a relatively high socioeconomic group, have had good lifelong nutrition, are in excellent general health, and have had prenatal care beginning in early pregnancy. They are also being cared for by obstetricians who feel more threatened by the legal profession.

The Whittier study does not detract from Dr. Davidson's thesis that policy changes are in order. In fact, it emphasizes the need for such changes.

Dr. C. Donald Christian, Tucson, Arizona. I do not need to remind the members of this group that women's health care is held in third place. Whether it is men or children first, I am not sure. It is true that if any of the entitlement programs are cut, it is prenatal care first and second are delivery and in-hospital care.

We are always imposed on by hospital administrators to decrease our costs, yet they ask us to provide intensive care for mother and baby and it is simply called "labor and delivery." We must do fetal monitoring and stress testing, but the same tests and monitoring done on a cardiac unit are called "intensive care." The dollars are not equally divided for equal services.

Dr. Donald H. Minkler, Berkeley, California. I would like to ask Dr. Davidson about the extent to which he has considered age-specific fertility in anticipating the need for specialized obstetric services in the 1980s?

Dr. Charles Plows, Anaheim, California. As Chairman of the Medi-Cal Committee of the California Medical Association, one of the big problems with the Medi-Cal obstetric patient is access. The programs of the State of California are overpromised and underpaid.

It is known that only 10% of physicians in California take Medi-Cal patients. Until we can get the other 90% involved in an appropriate prenatal care and delivery system, the problem will continue to exist.

Dr. Thomas Kirschbaum, Bethesda, Maryland. Dr. Davidson, would you comment on confounding relationships in your study with prenatal care? Specifically, if you would set aside a group of women who have no prenatal care, you also define a population with relatively little money and poor access to the health system and different attitudes toward personal health—illegal immigrant status and all the rest. Some investigators have found that when they correct for those things the apparent advantage of prenatal care diminishes or disappears. Finally, in support of what Dr. Christian said, if the President passes or signs the National Institutes of Health Appropriation Bill, which is currently before him, this will be the second straight year when the Child Health and Human Development Institute gets the smallest portion of increase of all.

Dr. Davidson (Closing). Let me answer in the reverse order. One, in terms of the issue of correcting other variables outside prenatal care and whether or not prenatal care will then make any difference, the result of an ongoing study by the Institute of Medicine and correcting for all of these variables shows that prenatal care will reduce perinatal mortality. If the quality of prenatal care is added, which is implied by the number of visits, plus the entrance of care in the first trimester, the improvement of prenatal care in reducing perinatal mortality is even more obvious. There is a more obvious reduction in the indigent care for perinatal services but the problem about how the health care dollar is going to be distributed with prospective payment is going to be a much broader issue than the amount of the dollar. Dr. Minkler asked if the data would indicate the number of pregnancies according to age. Is this a reflection of a general national trend toward an older population? That is true in regard to the lesser number of adolescents. There is a smaller denominator group but there is also a decreasing birth rate in that group, which reduces the total aggregate numbers even more. On the other hand, there appears to be a tendency not only toward an increasing age of the population but that older women are selectively increasing the birth rate in those over age 30 in contrast to previous years. In regard to some of the comments by Dr. Christian, I think his looking at intensive care as a part of labor and delivery room experience is an important example of how more specific economic studies need to be conducted to document that as a fact. There are a lot of economic studies justifying costs for renal dialysis and cardiovascular disease, and almost all of us know what it costs for a heart transplant. I would suggest we start looking more critically at these facts in terms of advancing these arguments. I would like to thank Dr. Sack for providing me with the text of his discussion. The question of whether age is the major variable is important and I would suggest to him that in some instances age is specifically identified with the risk as it pertains to genetic disease. This is the basis for most of our genetic counseling and diagnosis. There is a higher incidence of certain medical conditions that increase with age. He indicated six perinatal deaths represented in his group, which equals a perinatal mortality rate value of 14 in that group. This is not significantly different from the perinatal mortality value of 17 in our group of a similar age. The cesarean section rate he noted was 29.7% as compared to our 22.9%, which is also not significantly different. He did have a significantly higher incidence of primary cesarean sections, 61% in the elderly primigravid woman as compared to our 41%. On the other hand, his 12.5% primary cesarean section rate in those over 35 is not significantly different compared to our 15%. I agree that factors other than age contribute to poor pregnancy outcome, most notably socioeconomic status. This is especially true when rates of low–birth-weight infants are compared. The Whittier group had 3.1% low–birth-weight infants and ours had 8.3%. That is statistically different; however, our data show that this perinatal mortality rate in the lower socioeconomic group can be reduced with maternal and neonatal care. This is a point to be emphasized when looking at increasing health costs. In conclusion, it is more beneficial to look at how one packages care and that providing prenatal care is especially important in the groups that are at high risk for complications.

Intraperitoneal chemotherapy for advanced ovarian cancer

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Treatment of patients with advanced ovarian cancer who have failure of first-line chemotherapy is rarely effective. Preliminary pharmacokinetic and phase II clinical studies established the feasibility of delivering relatively high concentrations of cisplatin intraperitoneally via a semipermanent catheter, while using intravenous sodium thiosulfate as a neutralizing agent to decrease the nephrotoxicity of cisplatin. Sixty patients with advanced ovarian cancer, all of whom had failure of first-line chemotherapy (including cisplatin in 56 of 60), were treated with high-dose intraperitoneal cisplatin in combination with doxorubicin and/or cytarabine. Of the 46 patients evaluable for response, 19 (42%) showed an objective response, most often (12/19) disappearance of malignant ascites. No serious drug-associated morbidity was observed aside from three cases of intestinal obstruction which may have been due in part to drug-induced adhesions. It is felt that prospective studies to compare the efficacy of intraperitoneal chemotherapy with other forms of "salvage" therapy, as well as its use as initial chemotherapy for advanced ovarian cancer, need to be done. (AM J OBSTET GYNECOL 1985;152:474-8.)

Key words: Ovarian cancer, intraperitoneal chemotherapy

Treatment of ovarian cancer that persists after aggressive operation and systemic chemotherapy is often ineffective. Alternative systemic chemotherapeutic regimens are rarely successful and abdominal irradiation can be expected to benefit only those patients with minimal residual disease, often at the cost of substantial morbidity.

In a search for better strategies to control persistent or recurrent ovarian cancer, a system for delivering high concentrations of specific chemotherapeutic agents intraperitoneally via a totally implanted peritoneal access catheter has been developed.[1] Preliminary pharmacokinetic studies with cisplatin,[2] one of the most effective drugs currently available to treat ovarian cancer, showed that intraperitoneal administration could achieve local levels many times higher than those achievable in plasma. It was also shown that concurrent systemic administration of sodium thiosulfate could prevent nephrotoxicity. A preliminary phase II clinical trial of intraperitoneal cisplatin in combination with doxorubicin and cytarabine suggested an objective response rate of 35% to 45%.[3] The present report describes the results achieved with intraperitoneal chemotherapy in a larger group of patients with refractory ovarian cancer.

Methods and clinical material

The study population comprised 60 consecutive patients with refractory ovarian cancer. All patients signed an informed consent approved by the Human Subjects Committee, University of California (San Diego) School of Medicine.

The major characteristics of these cancers in terms of stage, grade, and histologic type and the amount of disease present at the time intraperitoneal therapy was begun are as shown in Tables I to IV.

Fifty-six of 60 patients had received multiple courses of cisplatin and cyclophosphamide and 53 patients had received doxorubicin in addition. Four patients had received an alkylating agent alone or in combination with 5-fluorouracil, methotrexate, and hexamethylmelamine.

At the time of referral for intraperitoneal therapy, 42 patients had ascites and/or tumor masses known to be >2 cm in diameter. Eighteen patients had tumor masses <2 cm in diameter or positive cytologic results only. In addition to having failure of front-line chemotherapy, patients had to have recovered from any toxicities attributable to prior therapy and have a life expectancy of >2 months. Values for serum creatinine had to be ≤1.5 mg/dl, bilirubin <3.0 mg/dl, white blood cell count ≥3000/mm³, and platelet count ≥100,000/mm³.

All patients either had a semipermanent catheter

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Table I. Initial stage of disease

Stage	*No. of patients*
IC	1
IIB	3
III	44
IV	12

Table II. Tumor grade

Grade	*No. of patients*
1 (well differentiated)	6
2 (moderately differentiated)	20
3 (poorly differentiated)	34

(Tenckhoff or Toronto Western Hospital) attached to a subcutaneously implanted reservoir (Port-a-Cath) placed into the peritoneal cavity prior to beginning the treatment program or were treated by the percutaneous placement of a peritoneal dialysis catheter with each treatment course. Access to the reservoir of the semipermanent catheters was via a 19-gauge Huber needle inserted percutaneously after careful antiseptic preparation of the overlying skin. Port-a-Cath peritoneal portals and 19-gauge Huber needles were purchased from Pharmacia Nu Tech, Piscataway, New Jersey; Tenckhoff catheters were purchased from Cobe Laboratories, Inc, Lakewood, Colorado; Toronto Western Hospital catheters were purchased from Accurate Surgical Instruments Co., Toronto, Ontario, Canada.

The first 15 patients were treated with three drugs, including cisplatin at a dose of 100 or 200 mg/m^2 along with sodium thiosulfate, cytarabine at a dose of 500 mg/2 L (10^{-3}mol/L), and doxorubicin at a dose of 20 or 2 mg/2 L treatment volume. The 20 mg dose of doxorubicin was abandoned early in the trial because of an unacceptable level of abdominal pain.

The next 45 patients were treated with cisplatin, either 100 or 200 mg/m^2, with cytarabine given at a dose of 2000 mg (4×10^{-3}mol/L) in the 2 treatment volume. All patients received intravenous sodium thiosulfate, 4 gm/m^2 as an initial bolus and 12 gm/m^2 as a 6-hour infusion beginning at the initiation of the chemotherapy instillation. The drugs were administered as rapidly as possible and remained in the peritoneal cavity for 4 hours, at which time an attempt was made to remove as much of the fluid as possible. All patients received overnight hydration prior to treatment. Therapy was repeated at 21- to 28-day intervals, depending on the patient's recovery from any toxicity of therapy. An intensive antiemetic regimen was used as part of this treatment program. Unfortunately, in spite of this antiemetic program, nausea and vomiting were quite significant.

Table III. Results of histologic examination

Type	*No.*
Serous cystadenocarcinoma	39
Solid adenocarcinoma	13
Endometrioid	4
Mucinous	4

Table IV. Amount of disease present at start of intraperitoneal chemotherapy

Aggregate masses <2 cm in diameter, no ascites	18
Aggregate masses >2 cm and/or ascites*	42

*Three patients with ascites had aggregate tumor masses <2 cm in diameter.

Table V. Favorable response to intraperitoneal chemotherapy

Type of response	*No. of patients*	*Duration (mo)*
Disappearance of ascites	12	3-7+
Decrease in size of masses	4	3-20+
Conversion of cytologic results, positive to negative	2	4-8+
Pathologic complete response	1	9

Results

Of the 60 patients, 14 are not evaluable for response at this time. At the time of insertion of the intraperitoneal catheter in these patients the presence of persistent cancer had been documented by biopsy or cytologic testing, but no disease was detectable by noninvasive techniques. To date there is no clinical evidence of active disease in this subgroup with follow-up ranging from 4 to 19 months (average 11 months) since the beginning of intraperitoneal chemotherapy.

Among the 45 evaluable patients, 19 (42%) showed an evaluable response to intraperitoneal chemotherapy (Table V). Responses related to initial stage of disease, grade of disease, and amount of residual disease are shown in Tables VI to VIII.

A total of 248 courses of intraperitoneal chemotherapy are evaluable for toxicity. Only six courses (2.5%) were associated with a serum creatinine rise to >1.5 mg/100 dl. In each case the patient had been heavily pretreated with cisplatin and in all cases the value returned to baseline within several weeks.

White blood cell counts dropped below 2000/mm^3 following only four courses, with platelet nadirs of <75,000/mm^3 being observed following 5% of courses. In no case did a patient require platelet transfusions or hospitalization for complications of leukopenia.

Two patients developed culture-proved bacterial peritonitis. They both recovered completely with catheter removal. Thirteen courses of therapy were asso-

Table VI. Tumor grade and response to intraperitoneal chemotherapy

Grade	*Response*	*No response*	*Not evaluable*
1	2	—	4
2	6	9	5
3	11	18	5
Total	19	27	14

Table VII. Amount of residual tumor and response to intraperitoneal chemotherapy

	Response	*No response*	*Not evaluable*
Masses <2 cm, no ascites	2	4	12
Masses >2 cm and/or ascites	17	23	2
Total	19	27	14

Table VIII. Initial stage of disease and response to intraperitoneal chemotherapy

Stage	*Response*	*No response*	*Not evaluable*
IC			1
IIB	2		1
III	14	21	9
IV	3	6	3
Total	19	27	14

ciated with fever without any evidence of infection. Significant local pain, defined as lasting longer than 72 hours or requiring narcotic analgesia, developed following 60% of treatment courses with the 20 mg dose of doxorubicin, in 20% of courses with the 2 mg doxorubicin dose, and in fewer than 10% of courses when doxorubicin was not included in the treatment regimen.

Adhesions following intraperitoneal chemotherapy have resulted in 55% of the catheters becoming one-way valves within 6 months. Three patients, two responders and one nonresponder, have required operation for intestinal obstruction due to adhesions. Two of these three patients had received intraperitoneal doxorubicin.

Comment

Pharmacologic modeling has suggested that direct intracavitary administration of certain chemotherapeutic agents by dialysis may result in a much greater drug exposure for the tumor than intravenous administration of the same drugs.[4] Specifically, drugs with low clearance rates from the peritoneal cavity and high clearance rates from the systemic circulation will demonstrate this phenomenon.

Two major potential benefits may result from such a therapeutic approach to malignancies localized to body cavities. First, if the efficacy of a particular agent were concentration-dependent, then direct intracavitary therapy resulting in increased local drug concentration might improve antitumor response. Second, if a drug would be metabolized into a nontoxic form prior to entry into the systemic circulation during passage through the liver or upon entry into the plasma by the administration of a neutralizing agent, toxicity might be reduced.

Several drugs have been investigated for intraperitoneal administration. Cisplatin has been delivered safely in a dose of up to 270 mg/m^2 with simultaneous intravenous sodium thiosulfate.[1] Thiosulfate was selected as a neutralizing agent on the basis of its ability to protect against cisplatin-induced renal toxicity in a murine model.[5] It is thought to react covalently with cisplatin, with the resulting complex not being toxic or possessing antitumor activity.[5]

Not only has a pharmacokinetic advantage for peritoneal cavity drug exposure been demonstrated, but the systemic delivery of active cisplatin is increased twofold (at an intraperitoneal dose of 270 mg/m^2) over that observed with an intravenous dose of 100 mg/m^2.[1]

Following in vitro demonstration that ovarian carcinoma is sensitive to concentrations of cytarabine achievable during intraperitoneal chemotherapy, the safety and efficacy of cytarabine in vivo, when administered by 5-day dialysis exchange, was demonstrated.[6]

In this report we have described our initial experience with combination intracavitary chemotherapy in patients with refractory ovarian carcinoma. The response rate of 42% in this high-risk group of patients, all of whom had received intensive systemic chemotherapy, appears to be at least as favorable as alternative salvage regimens. It is noteworthy that 17 of 40 evaluable patients (42%) with ascites and/or residual tumor masses >2 cm in diameter showed a favorable objective response. This latter group rarely benefits from abdominal irradiation or alternative systemic chemotherapy regimens after prior intensive treatment with cisplatin. It is also noteworthy that response rate does not appear to be related to tumor grade (Table VI).

Fourteen patients known at the time of initiation of intraperitoneal chemotherapy to have residual cancer, not evaluable by noninvasive techniques, have been followed up from 4 to 19 months without clinical evidence of recurrent disease. Since this is the same group of patients who are most likely to benefit from whole abdominal irradiation, long-term follow-up should yield preliminary information regarding the relative merits of these two forms of "rescue" therapy for systemic chemotherapy failures.

An unresolved problem is the occurrence of adhesions following intraperitoneal chemotherapy. Approximately half of the catheters have become one-way valves within 6 months of placement, permitting introduction of fluid but not removal. Instillation of 32% dextran 70 at the time of initial catheter placement and after each course of chemotherapy has not been very effective in preventing adhesions. There is some evidence that nonsteroidal anti-inflammatory drugs such as ibuprofen may be of some value in preventing adhesions.[7] The theory on which this therapy is proposed is that since arachidonic acid metabolites mediate the acute fibroproliferative inflammatory response following surgical trauma, high doses of an anti-arachidonic acid agent should suppress this response. It is to be hoped that appropriate clinical trials will fulfill this premise. Our current protocol includes the use of ibuprofen, 600 mg three times a day, starting at the time of catheter placement.

Since this was a pilot study, future studies are needed to define the optimal drug combinations, concentrations, and schedules for intraperitoneal chemotherapy. Eventually randomized controlled clinical trials comparing the intraperitoneal route to systemic administration as the initial mode of chemotherapy for ovarian cancer will need to be done to determine whether the pharmacokinetic advantage achieved by the use of this form of therapy can be translated into increased response rates and longer periods of disease-free survival.

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Discussion

DR. EDWARD C. HILL, San Francisco, California. I am particularly pleased to be able to discuss this paper, not only because Dr. Lucas and his colleagues are pioneering new methods of chemotherapy in the treatment of advanced ovarian carcinoma but also because it allows me to acknowledge publicly my appreciation to him for allowing me to spend a day earlier this year in observing and learning his technique in establishing a delivery system for the administration of prolonged intraperitoneal chemotherapy.

Finding residual disease in the peritoneal cavity following what appears to be a complete remission in response to systemic chemotherapy is an extremely disappointing experience to the clinician and is particularly devastating to the patient who has hopes of a cure. Despite excellent immediate results from surgical debulking and systemic chemotherapy, the long-term results are less than anticipated, and there is little evidence to date that the 5-year survival rates in ovarian epithelial malignancies have been significantly influenced by these methods. Most patients with ovarian malignancy still present initially with widespread peritoneal metastases and, unless all the tumor is removed or destroyed, will die of the disease within a few years. The age-adjusted death rate for ovarian cancer has increased from 3/100,000 female population in 1930 to 13 in 1975.[1] Although the immediate survival and the quality of life are improved by treatment that takes into consideration such factors as tumor volume, histologic grade, and location of metastases, the odds that a patient with Stage III disease will be living in 5 years are still <10%.

Ovarian cancer tends to remain localized to the peritoneal cavity. Because of this, attempts have been made to increase the local concentration of chemotherapeutic agents by intraperitoneal administration. Twenty years ago, thiotepa was being introduced into the peritoneal cavity, but it became evident that this particular agent was not activated until it had been absorbed into the bloodstream and carried to the liver. However, much has been learned about the pharmacokinetics of these agents since that time. In 1978 Jones et al.[2] reported that there was a tenfold to thirtyfold difference in concentration between intraperitoneal and plasma levels when methotrexate was administered intraperitoneally. Studies since that time have indicated there are distinct advantages to intraperitoneal administration of cisplatin, Adriamycin, and 5-fluorouracil with greater tumor exposure to the drugs and less exposure of the peripheral tissues and therefore less toxicity.

Dr. Lucas' report today shows that effective combination chemotherapy with cisplatin and cytarabine can be administered to patients with disease that is refractory to systemic therapy and, furthermore, that this can be accomplished with relative safety and acceptable levels of toxicity. He has found that Adriamycin in a 20 mg dose injected into the peritoneal cavity, even though it is dissolved in a large volume of fluid, cannot be used because of severe abdominal pain. He has demonstrated that bacterial contamination of the peritoneal cavity and extensive adhesion formation with possible bowel obstruction are complications that should be watched for and may be preventable. Finally, he has pointed out that this is an experimental approach with much more work to be done in order to determine whether the intraperitoneal mode of administration can be improved in patients with persistent disease and if it might be advantageous as first-line therapy.

Several questions come to mind. First, would you describe the antiemetic program used in this study? Second, with reference to the 46 evaluable patients, was there any relationship between the histologic grade of the tumor or the length and type of previous systemic chemotherapy and the presence or lack of a response to intraperitoneal therapy? Finally, in the 19 patients in whom a response was noted, can you give us some idea as to the mean duration of the responses?

I wish to thank the essayist for sharing with us his experience and his insights. Only by continuing and supporting this type of clinical investigation can significant advances be made in the management of the most dread of all gynecologic disorders—ovarian cancer.

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Dr. Paul Morrow, Los Angeles, California. This is one of the most promising techniques that has come along in treating ovarian cancer. I have a question about your results because 12 of these 17 responders were measured in terms of control of ascites. As you know, there are a number of agents that can be put into the peritoneal cavity that are not known to be antitumor drugs, for example, tetracycline, which can control ascites. In the Gynecologic Oncology Group for example, control of serous effusion is no longer used as an indication of response. I wonder if you would comment about that.

Dr. Jack Stapleton, Reno, Nevada. I have two questions. One is in reference to the possibility of using intraperitoneal baths as primary therapy. Do you think that at the conclusion of operation it is best to leave in an intraperitoneal tube or catheter for just an initial bath and subsequently place the patient on a regimen of systemic therapy? Second, did you notice any increase in complications in patients who received intraperitoneal chromic phosphate?

Dr. Lucas (Closing). I appreciate Dr. Hill's comments. Our antiemetic regimen has been the popular "shotgun" approach with Decadron, droperidol, metoclopramide, hypnosis, deconditioning, and anything else that might possibly work, but it is basically three agents in combination: Decadron, droperidol, and metoclopramide. Dr. Hill asked about the type of previous chemotherapy. That is a very significant point to readdress because 56 of 60 patients had previously been treated with multiple course of cisplatin. You might expect a very low response rate to intraperitoneal cisplatin, so any response rate would tend to be looked at favorably. Again, this is a preliminary pilot study. The duration of response rates cannot be determined with accuracy because we have not reached our end points in some groups, particularly the patients who had minimally evaluable disease. To answer Dr. Morrow's question with regard to ascites, I think that ascites can be treated in a number of different ways. The question is what is the response rate with other methods compared to our method? Sixteen of these patients had little or no evaluable disease. The rest of these patients were considered end-stage failures. We had patients coming in from a number of areas and some of them were on the border of having obstruction. It was a subjective evaluation to judge whether they had 2 months' life expectancy. I can think of a number of patients who had failure of first-line chemotherapy, second-line chemotherapy, and irradiation and responded for quite a long period of time. I think that ascites control should be looked at very carefully in terms of validity of being an objective criterion. To answer Dr. Stapleton, I think the application of this technique as primary therapy is very logical and needs to be explored. Perhaps a compilation of data from around the country from various groups who are using this or similar techniques needs to be completed before we embark on its use as primary therapy. We do have a protocol that is approved by the Human Use Committee for front-line chemotherapy and has a very logical place in the treatment after surgical debulking of the tumor. The second question—we do not have any patients who have had previous chromic phosphate but we would not hesitate to use it.

The Zavanelli maneuver: A potentially revolutionary method for the resolution of shoulder dystocia

Eugene C. Sandberg, M.D.
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Shoulder dystocia is a perilous complication for the fetus. Suffocation and death are imminent. For the obstetrician, there is insufficient time for consultation. Either he or she is ready with an array of manipulative remedies for sequential application or a disorganized chaos will ensue and chance will determine the outcome. Worthy accoucheurs will have planned for this event and will have selected from the numerous procedures touted for its correction that group he or she intuitively feels will be most effective or, at a minimum, most easily remembered. The Zavanelli maneuver deserves to be on every obstetrician's list. It must occupy a bottom priority, however, until its virtue and applicability, demonstrated to date in but a single case, can be confirmed. All current maneuvers for the treatment of shoulder dystocia are directed to completion of vaginal delivery. The Zavanelli maneuver is predicated on cephalic replacement with subsequent delivery by cesarean section. (AM J OBSTET GYNECOL 1985;152:479-84.)

Key words: Pregnancy, shoulder dystocia, Zavanelli maneuver

Although anticipation of shoulder dystocia (Table I) and its prevention, when practical, are useful and should be applied by all, "impaction" of the anterior fetal shoulder can occur unexpectedly in the experience of even the most thoughtful obstetrician. When it does, the fetus is immediately imperiled. Its oxygen supply is suddenly severely restricted or eliminated. Its delivery must be effected within the next several minutes if its life is to be preserved. There is insufficient time for contemplation, for reading an obstetric text, or even to call for consultation. Assistance may occasionally, or even commonly, be available and should be called for, but neither its presence nor its quality can be relied on. Consequently, every birth assistant, whether student, resident, midwife, family practitioner, or obstetric specialist, should have prepared for this moment by developing and memorizing a sequence of maneuvers that he or she intends to use in this situation. Those who have not will sweat and blunder and automatically subject the pregnant woman to a greater than necessary potential for traumatic injuries and the fetus to hypoxic residua or death.

The maneuvers that have been effective in the hands of various obstetricians in overcoming shoulder dystocia are described in Table II. To these can now be added a wholly different procedure, one based on a principle diametrically opposite to that underlying all previously reported maneuvers. In the past, treatment for shoulder dystocia has invariably been directed to completion of the delivery process, with all efforts being designed to enhance fetal expulsion. The Zavanelli maneuver, on the other hand, is predicated on reversal of the delivery process, with return of the fetal head to its previous intravaginal location and extraction of the fetus by cesarean section as soon as practical thereafter.

Table I. Anticipation of shoulder dystocia: Commonly associated conditions

Obesity
Multiparity
Postmaturity
Previous delivery of large infant or history of shoulder dystocia
Large infant by manual or ultrasound estimation
Small or borderline maternal pelvis
Pelvic deformity
Slow descent of the fetal head
Prolonged second stage
Necessity for midforceps delivery

Case report

S. F., a 30-year-old Caucasian woman, was first seen on June 16, 1977, during the tenth week of her second gestation, by Dr. William Zavanelli of Pleasanton, California, who cared for her throughout her pregnancy and delivery. Her previous pregnancy had resulted in the vaginal delivery of a normal, 8-pound 10-ounce (3912 gm), female infant after 10 hours of labor in the fortieth week of gestation 6 years earlier.

Physical and laboratory examinations were normal and manual mensuration revealed a gynecoid pelvis with normal obstetric diameters. The patient weighed 188 pounds when first seen and 225 pounds at the time

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Table II. Methods described for the treatment of shoulder dystocia

- I. Maneuvers to deliver the anterior shoulder anteriorly
  - A. Pressure on the anterior side of the fetal face and neck
    - 1. Toward the floor, resulting in traction on the anterior shoulder
    - 2. Upward and backward toward the hollow of the maternal sacrum, to simultaneously apply traction to the anterior shoulder and potentially to superiorly displace the posterior shoulder[1]
  - B. Pressure in suprapubic area
    - 1. Directly posteriorly, to force the anterior shoulder behind the pubic bone[2]
    - 2. To one side of the maternal abdomen or the other or alternately,[3] to force the shoulders into an oblique diameter of the pelvis
  - C. Pressure on the uterine fundus to supplement expulsive forces (Kristeller expression)
  - D. Insertion of the index and middle fingers into the vagina behind the pubic bone (palm up) to form a groove or trough through which the anterior shoulder may descend with fundal pressure[4] (principal action may be posterior displacement of the anterior shoulder)
  - E. Insertion of a shoehorn-like instrument between the anterior shoulder and the posterior surface of the pubic bone along which the anterior shoulder may descend with fundal pressure[5] (principal action may be posterior displacement of the anterior shoulder)
- II. Maneuvers to deliver the posterior shoulder anteriorly (rotational maneuvers)*
  - A. Pressure with two or more fingers on the anterior aspect of the posterior shoulder or axilla, with 180-degree rotation of the shoulder in the direction of the fetal back[6]
  - B. Pressure with two or more fingers on the posterior surface of the more accessible shoulder (possibly the anterior but usually the posterior), with 180-degree rotation of the shoulders in the direction of the fetal chest[3]
  - C. Insertion of two or more fingers into the posterior axilla of the posterior shoulder, with subsequent traction plus 180-degree rotation of the shoulders in the direction of the fetal chest[7]
- III. Maneuvers to deliver the posterior shoulder and arm posteriorly
  - A. Insertion of the hand (palm to fetal chest) to grasp, flex, and extract the posterior arm[7]
  - B. Extraction of the posterior arm followed by 180-degree rotation of the shoulders by traction on the extracted arm (toward the fetal back[8] or toward the fetal chest, with or without subsequent manual extraction of the newly created posterior arm)
- IV. Maneuvers to decrease the bisacromial diameter
  - A. Deliberate fracture of the anterior or posterior clavicle
  - B. Anterior or posterior cleidotomy
- V. Symphysiotomy

*Rotational maneuvers are commonly considered to be more effective when combined with suprapubic and/or fundal pressure.

of delivery on January 18, 1978. Her prenatal course was otherwise within normal limits.

The patient was admitted to the hospital at 40½ weeks' gestation in spontaneous, but early and desultory, labor. Membranes were intact, the cervix was 4 cm dilated, and the obviously large fetus was presenting by the vertex at the −2 station. A few hours later, after failure of productive contractions to develop, the membranes were artificially ruptured and augmentation of labor was initiated by intravenous oxytocin. Labor proceeded progressively thereafter, the cervix becoming completely dilated within 4½ hours.

Following 1½ hours of second-stage labor with good contractions and a steadily increasing station, delivery of the head occurred spontaneously over a right mediolateral episiotomy from the occipitoanterior position with the mother under pudendal block and local perineal anesthesia. Restitution developed but no further descent occurred, the base of the infant's head being tightly applied to the vulvar tissues. Shoulder dystocia was evident. Standard downward pressure on the anteriorly directed side of the fetal face and neck was applied but was unproductive. Suprapubic pressure was then applied, but this also was unsuccessful in effecting delivery of the anterior shoulder. Two fingers were then inserted into the vagina and rotatory force was applied to the anterior surface of the posterior shoulder. No substantial rotation could be achieved. An attempt was then made to introduce a hand into the vagina with the intention of extracting the posterior arm. However, the apposition of fetal and maternal tissues was too tight to permit entry. In desperation, an attempt to reverse the mechanism of labor was undertaken. The vertex was manually rotated and the head was returned to its prerestitution position at full extension in a direct occipitoanterior position (Fig. 1). The head was then manually flexed, recapitulating, in reverse, the birth of the head by extension (Fig. 2). The intention was to then apply upward pressure to force the head into the vagina. The latter maneuver was unnecessary, however, as the head recoiled into the vagina instantly and effortlessly upon completion of flexion. The fetal head was estimated to have been outside the vagina for 2 to 2½ minutes.

The fetal heart rate, normal before delivery of the head, was noted to be normal immediately after its reinsertion as well. No significant uterine contractions and no appreciable abnormalities of the fetal heart rate were observed in the next 60 minutes during which the anesthesia and nursing teams were assembled and the patient was transported to the operating room in preparation for cesarean section. The episiotomy was closed during this interval, no extension or lower vaginal lacerations being noted.

A female infant weighing 12 pounds, 2 ounces (5500 gm) was delivered by low transverse cervical cesarean section 67 minutes after reinsertion of the fetal head. Ketamine–nitrous oxide–succinylcholine and endotracheal intubation were used to produce anesthesia. The infant was normal in appearance, showed no evidence of either injury or congenital abnormalities, and had Apgar scores of 7 at 1 minute and 10 at 5 minutes. Estimated blood loss at cesarean section was 1500 ml, 1000 ml of which was replaced by transfusion of whole blood.

Oral ampicillin was administered prophylactically

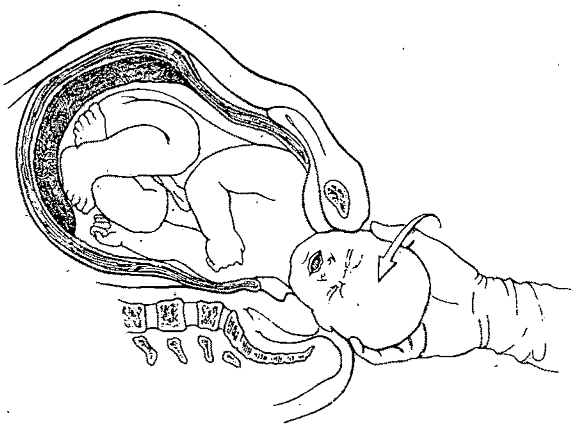

Fig. 1. Diagram of first part of the Zavanelli maneuver. If restitution has occurred following expulsion of the head, as in this case, the head is first manually returned to its prerestitution position, full extension in a direct occipitoanterior position.

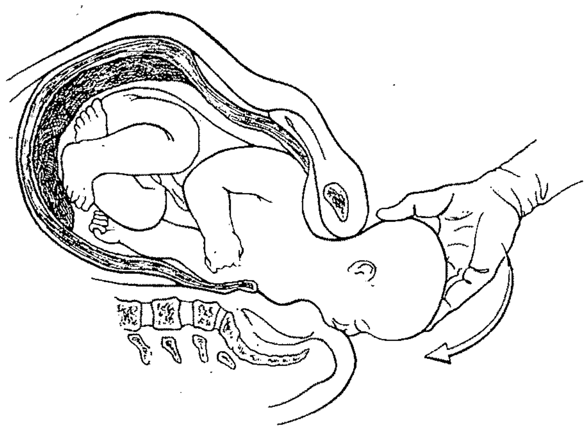

Fig. 2. Diagram of second part of the Zavanelli maneuver. The head is manually flexed recapitulating, in reverse, the birth of the head by extension. Upward pressure to recapitulate expulsion, in reverse, was not required in this instance.

during postpartum hospitalization. The patient exhibited a temperature of 100.8° F at 8:00 PM on the first postpartum day. She was afebrile at all other times during her hospitalization and the postpartum course was uneventful. She was dismissed on the fifth postoperative day. The infant's hospital course was equally uneventful. The child has been observed regularly during the ensuing 6½ years and its development has been completely normal.

Comment

This is the first formally published description of what can appropriately be called the Zavanelli maneuver for the management of shoulder dystocia. Litt[9] made mention of this maneuver approximately 3 years after its use in the case reported here, while propounding a question regarding another aspect of shoulder dystocia. Its application was said to have been followed by abdominal delivery of a dead infant and subsequent "hysterectomy for sepsis." Neither the particulars of the case nor the basis for the poor result was described. To my knowledge, no other information regarding this technique or the effects of its use have been published.

The fact that the Zavanelli maneuver was successful in this situation in which several of the venerated maneuvers for the treatment of shoulder dystocia were attempted and proved to be ineffective suggests that this manipulative procedure may have more potential than is likely to be accorded to it on first consideration. That it was additionally conducted without traumatic injury to either the pregnant woman or the fetus serves to reemphasize this point.

Different concepts have been offered regarding the attitude and position of the fetal shoulders at the time of their "impaction." Common teaching holds that, with vertex presentation, the fetal head descends in the transverse position, during which the bisacromial diameter parallels the anteroposterior midline of the maternal pelvis. While the fetal head is undergoing flexion, descent, internal rotation, birth by extension, restitution, and external rotation, the shoulders are generally considered to engage and descend in either the anteroposterior or an oblique diameter of the maternal pelvis. When anterior shoulder impaction eventuates, the anterior shoulder is overriding the superior aspect of the pubic bone in the midline, or is unengaged and lying in an oblique diameter, or is engaged in an oblique diameter and is unable to descend further or to rotate internally. Regarding the posterior shoulder, some authors have considered that when anterior shoulder impaction occurs, the posterior shoulder is held above the level of the sacral promontory. Others maintain that it is compacted firmly and tightly in the hollow of the sacrum. It is possible that both groups are correct and that in one instance one situation prevails and in another the other. No formal suggestion of this possibility seems to have been declared, however, and no method has been developed by which these possible situations might be differentiated. Consequently, no contrasts have been drawn between existing maneuvers as to which may be the more appropriate in a given situation. For example, it may be that the rotational and posterior arm extraction maneuvers would be more applicable for situations in which the posterior shoulder has descended deeply into the maternal pelvis. On the other hand, the maneuver described by Hibbard[1] and that described in this report might intuitively be thought to be more expeditious in instances in which the posterior shoulder has remained unengaged.

That no single maneuver has been found to be regularly adequate for the relief of shoulder dystocia and that numerous maneuvers have been developed may result from the fact that fetal attitude and position differ from case to case. It is apparent from the obstetric literature that no organized study of this matter has been undertaken, probably because few obstetricians have had sufficiently repeated exposure to this abnormality. In any case, it is agreed by all who practice obstetrics that the presence in their repertoire of one or two maneuvers is inadequate for the potential problems to be faced with differing cases of shoulder dystocia. Most react to this by mentally accumulating the entire array of maneuvers or at least a significant proportion thereof.

The Zavanelli maneuver has particular appeal because of it simplicity, its ease of performance, and its unique divergence from the traditional vaginal delivery–oriented thinking behind all previously suggested maneuvers. It offers not only the potential of an additional therapeutic maneuver for a difficult problem but also a window into a new realm of obstetric thought.

While it is apparent to all that a single success proves little, the potential of the Zavanelli maneuver as a revolutionary or, at the least, an ancillary approach to the treatment of shoulder dystocia remains unassailable. The maneuver has been used successfully without traumatic injury to the fetus or the pregnant woman in a circumstance in which other maneuvers failed. Having been made aware of this fact, every individual who assists at childbirth should seriously consider adding the maneuver to his or her list of available methods for the management of shoulder dystocia, especially that which is severe and unremitting.

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Discussion

Dr. Lester T. Hibbard, Los Angeles, California. Dr. Sandberg has addressed one of the unsolved problems of obstetrics, giving us an excellent resumé of current practices and a dramatic description of an innovative and unique maneuver to rescue the fetus when conventional methods to deal with shoulder dystocia have failed.

Dr. Sandberg has nicely categorized our current strategies for dealing with shoulder dystocia, but he did not fully exhaust the subject. An additional method would be a measure to alter the architecture of the bony pelvis. For example, one could resort to the maneuver popularized in Texas by McRoberts, consisting of releasing the patient's legs from the stirrups and flexing the thighs sharply to reduce the angle between the sacrum and the spine.[1]

If this maneuver fails, as it sometimes will, a convenient next step would be to abduct the patient's legs to an 80-degree angle and proceed with a subcutaneous symphysiotomy. Symphysiotomy has been recommended by some authorities for shoulder dystocia, although admittedly without much enthusiasm or conviction.[2] Its logic is that, if properly performed, the pelvic capacity is increased as much as 25%. In addition, the short- and long-term complications are not as great as have been claimed,[3, 4] and it appears reasonable if the only alternative would be a damaged child.

However, symphysiotomy has never been accepted in the United States. I mention it only to compare it with Dr. Sandberg's more palatable suggestion. We have all mastered the art of a cesarean section. The only question is can the head really be replaced as easily as described? Having never tried it, I can offer no opinion. I do know of one incident that would serve as a testimonial. About 10 years ago, one of the members of our resident staff encountered unreducible double nuchal arms during the course of an attempted breech extraction. Being unburdened by the convictions of his elders, he stuffed the fetal torso back into the mother's birth canal and proceeded to a successful cesarean delivery. I would like to give proper credit to the individual who performed this prodigious feat, but I cannot remember his name and, so far, have been unable to locate anyone who will admit to the deed, although several have confirmed my recollection.

I commend Dr. Sandberg for calling the Zavanelli maneuver to our attention, and, since shoulder dystocia is seldom fully anticipated and incidents of permanent damage as a result of dystocia still occur, I am confident that others will avail themselves of the opportunity to test its feasibility.

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Dr. Robert C. Goodlin, Omaha, Nebraska. As a house officer, I collected cord blood from the infants of diabetic mothers at the various private hospitals as part of my research project. In one case, I scrubbed with Dr. William Stromme, the coauthor of *Operative Obstetrics,* and watched him attempt a breech delivery of a very large infant. As he reached the level of the fetal scapula, he simply shook his head and pushed the body of the fetus almost entirely up in the vagina. The woman had received a caudal anesthetic and, with the aid of a scrub nurse (he did not even ask me to help), he stood between the patient's legs and did a very rapid cesarean section, delivering the baby in apparently good condition.

Dr. Harold Lyons, Merced, California. I would make a point of historical precedence. The late, lamented Dr. Don de Carle was Potter-trained and a master at breech delivery. His ability was so great that it was a duty, a thing of beauty (?), and a joy to watch him deliver a breech fetus. Because of this ability, practitioners from the "hinterlands" of California were wont to travel to San Francisco to see Dr. de Carle do a breech delivery. In 1961, the year that he was president of this society, he told me the following story. A female general practitioner from the far reaches of the Sacramento valley came to San Francisco to see him perform a breech delivery, which he did. She was lavish in her praise, but at the end she said, "Dr. de Carle, what do you do if the legs and body are out and the head and shoulders won't come?" With some erudition he explained the possible maneuvers to her and she said, "Yes, Doctor, I had such a case, but nothing worked." He said, "What did you do?" She said, "Why, I just rushed the patient up to surgery, did a cesarean section, dragged the baby back through the birth canal, out through the uterus and abdominal wound, and the mother and child are doing fine." Now the point I wish to make is this, that if members of this society are to seriously pursue the Zavonelli procedure, then it behooves them to accord a modicum of approbation and accolade to that nameless, frightened, ill-trained, desperate, but brave, resourceful, unsung, unchronicled, yes even unpublished, precedent-setting "mother" of the first reverse, backward, upside-down Zavanelli procedure.

Dr. S. Gainer Pillsbury, Long Beach, California. I think all of us obstetricians agree that unexpected shoulder dystocia is one of the worst things we encounter. Most of us vividly remember every shoulder dystocia we ever had. The trick would be to identify which patients are going to have a shoulder dystocia prior to delivery. We would probably agree that cesarean section would be the best form of delivery. At Long Beach Memorial Women's Hospital we deal with a lot of diabetic patients, and they are managed by Dr. Roger Freeman who has instituted a policy of measuring the biparietal diameter and the diameter of the thorax prior to delivery and at term. If the diameter of the thorax exceeds the biparietal diameter by more than 1½, these patients are candidates for a cesarean section. The results of this study have not been collated yet; perhaps this could be a subject for an article in the future and I would like Dr. Sandberg to comment on that procedure.

Dr. Richard Taw, Los Angeles, California. Any manipulative procedure, especially from below, is much easier with a relaxed uterus. A patient under epidural or spinal anesthesia does not have a relaxed uterus, and it would be more difficult to do whatever you were planning to do with a tense or a contracting uterus. I had the misfortune of being on the other end of the stick in which a head was delivered and there was a spontaneous retrieval of the baby by the uterus. And I do mean retrieval. Of course there was a constriction ring. The woman had been in labor for some time and the head finally appeared in the perineum and it appeared that outlet forceps was indicated. We got the head out easily but when we took the forceps off, the head went back up inside. The answer to this problem was to relax the uterus. At that time, all we had to work with was chloroform. We called the head of the anesthesia department to give chloroform and the baby was easily delivered. I think in a situation like that, with the new drugs that the anesthesiologists have, you can get them to relax the uterus for you and you are more likely to succeed in your manipulation.

Dr. Charles Weber, La Jolla, California. There is a technique that has been used, although it has not been reported, which is called symphysiotomy. When we think of symphysiotomy, we think of the Gigli saw or doing some horrible distorting procedure that will make the patient incapacitated forever. The experience of a practicing missionary physician was reported to me. His answer to this whole problem of the large baby when he was practicing in the bush was simply to release the ligaments at the symphysis. You do not have to cut bones or anything else. He used a simple percutaneous incision that was extended down through the ligaments that separate the symphysis, and the baby was delivered easily. It is obvious these cases were not all shoulder dystocias, but some were head dystocias. The symphysiotomy accomplished the delivery without a large episiotomy. The incision was closed with only one or two stitches. The return of the ligamentous attachments comes readily. The orthopedists know this and this is one of their treatments for osteitis pubis and symphyseal discomfort. They release the ligaments between the two segments of the symphysis and the patient becomes comfortable, the ligaments are reestablished and she no longer has the pain. If any of us were brave enough to try this, it would be another method of handling shoulder dystocia. I do not think any one of us has thought of it—I know I have not.

Dr. Colin McCorriston, Honolulu, Hawaii. I have no personal experience with symphysiotomy but I worked with a very able physician who spent some time in New Guinea and was trained by some Australian people there. He learned to do symphysiotomies very well; however, they were used for breech delivery of the aftercoming head. He did not use a Gigli saw. He did the procedure subcutaneously with a sharp knife and retracted the urethra as he proceeded. He used a maneuver similar to McClavid's maneuver. The way to avoid a lot of pain and discomfort in the symphysis later is not to abduct the legs widely.

Dr. Sandberg (Closing). Dr. McCorriston and Dr. Weber, the technique of symphysiotomy you have both described was also mentioned to me recently by Dr. Albert Long in San Francisco. He concurred that the Gigli saw is unnecessary and that the same effect can be obtained simply by inserting a scalpel blade through the skin overlying the symphysis pubis and incising this cartilaginous material in the midline. This maneuver is simple, takes little time, does not customarily require additional effort, and effectively allows separation of the pubic bones.

I am very pleased by Dr. Taw's testimonial to the fact that retraction of the head into the pelvis following its delivery can and indeed has been seen to occur. I am also pleased to hear the several testimonials regarding rescue by reinsertion of undeliverable but partially born fetuses in a breech presentation. These anecdotal reports all seem to substantiate the general concept behind Dr. Zavanelli's intuitive move.

There is no question, Dr. Pillsbury, that anticipation and prevention is the best approach. I have no experience with the method of prediction you describe, but it sounds reasonable and we can all hope that testing will prove it to be beneficial. Anything that can sharpen our diagnostic ability and save us from getting into that perilous circumstance in highly desirable, not only for ourselves but obviously for the patient and particularly for the fetus.

Dr. Hibbard, Dr. William Zavanelli practices daily in Pleasanton, California, just across the San Francisco Bay from Stanford University. I hope that sometime you do get a chance to meet him as I think you will both profit. He is a Board-certified obstetrician/gynecologist who does a particularly able job of caring for the obstetric and gynecologic patients in his community.

I was intrigued when he described to me his method of management in this case a year or two ago. The image his description provoked has been with me ever since. I immediately felt that the maneuver had significant potential and could well be more broadly applied. I also felt that it deserved more attention and display than he modestly seemed willing to afford it. It deserved, I thought, to be presented in some public forum and offered to the medical community for evaluation and trial. Should the maneuver prove to be effective and ultimately added to our armamentarium, I would like very much to have Dr. Zavanelli receive the complete credit. It is wholly his maneuver and I have simply been the vehicle for its presentation.

Current Development

Neuroendocrinology of opioid peptides and their role in the control of gonadotropin and prolactin secretion

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Substantial evidence now exists to indicate that the endogenous hypothalamic opioidergic mechanism(s) represents one of the important controlling systems for release of gonadotropin-releasing hormone. Modulations of frequency and amplitude of the secretory activity of gonadotropin-releasing hormone appears to be mediated through an inhibitory action of endogenous opioids, and the functional coupling of the opioidergic and gonadotropin-releasing hormone systems is an ovarian steroid–dependent event. There is also evidence to implicate suprahypothalamic mechanism(s) that enhance endogenous opioid inhibition of secretion of gonadotropin-releasing hormone. Although exogenous opioid peptides and their synthetic analogs consistently induce the secretion of prolactin, blockade of opioid receptors in humans by naloxone failed to elicit a decrement in the levels of prolactin under a variety of conditions. On the contrary, naloxone induced a remarkable increment in the secretion of prolactin via an increased frequency of pulsatile release which is synchronized with pulses of luteinizing hormone. These observations suggest that a common neuroendocrine mechanism is involved in the opioidergic control of the secretion of both luteinizing hormone and prolactin in women. (AM J OBSTET GYNECOL 1985;152:485-93.)

Key words: Opioid peptides, gonadotropin-releasing hormone, reproduction

The discovery of opiate receptors in the brain led to the search for endogenous opioids, and in 1978, two pentapeptides, Met^5-enkephalin and Leu^5-enkephalin, were identified by Hughes et al.[1] These differ only by one amino acid at position 5, and it was noted that the amino acid sequence of Met-enkephalin corresponds to the 61 to 65 amino acid sequence of a 91 amino acid peptide, β-lipotropin. This observation provided a clue for the subsequent discovery of numerous larger opioid peptides, such as β-endorphin (31 amino acids), dynorphin 1-17, and many others. All of these peptides are now called opioid peptides because they have analgesic activity and bind to opiate receptor sites.

The localization of high concentrations of opioids, particularly β-endorphin in the human hypothalamus,[2] together with previous information on endocrine changes after the use of alkaloids, such as morphine, suggested that the endogenous opioids may have important interactions with hypothalamic neurons in the control of pituitary function. In this review, the role of endogenous opioid peptides in the regulation of reproductive function, such as the secretory activity of gonadotropins and prolactin, will be highlighted.

The opioid systems

Opioid precursors. The use of recombinant DNA techniques has made clear that opioid peptides, like many other peptide hormones, are not synthesized as separate compounds. Instead, a single gene encodes a large inactive polypeptide which contains within its structure the sequences of several small active molecules that are subsequently split from the precursor. There are three precursor proteins with several commonalities and composed of similar numbers of amino acids (257 to 265). They contain repetitive structures; for example, in proopiomelanocortin there are three melanocyte-stimulating hormone sequences; in proenkephalin A there are four copies of Met-enkephalin and one copy of Leu-enkephalin; and in proenkephalin B there are three sequences of Leu-enkephalin.[3-5]

Proopiomelanocortin, a glycopeptide, with carbo-

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hydrate attached near the N terminus of the molecule, was the first precursor to be identified. Proopiomelanocortin polypeptide is made in the anteror and intermediate lobes of the pituitary gland, in the hypothalamus and other areas of the brain, and in several peripheral tissues, including the placenta, gastrointestinal tract, lungs, and reproductive tract.[3] Unlike in other species studied, proopiomelanocortin-derived peptides are present in human adrenal medulla.[6] Processing of proopiomelanocortin to release its peptide fractions appears to be tissue specific. In the pituitary gland, the predominant products are β-lipotropin and adrenocorticotropic hormone (ACTH), with only a small portion of β-lipotropin subdivided to release β-endorphin.[7] Transcription of the proopiomelanocortin gene in the anterior lobe is in part regulated by glucocorticoids, which thus turn off the production of ACTH by inhibiting transcription of the proopiomelanocortin gene. The processing of proopiomelanocortin probably yields mostly β-endorphin in the brain and β-endorphin and α-melanocyte-stimulating hormone in the human adrenal medulla. In the intermediate lobe of the pituitary gland but not in the brain, β-endorphin is a α-N-acetylated, a step that completely abolishes the opiate-like activity of the peptide.

Pituitary tumors that produce Cushing's disease and the ectopic ACTH-producing tumor that causes Cushing's syndrome have been shown to relate to the presence of a proopiomelanocortin system.[8, 9] This is consistent with the observation of production and secretion of β-lipotropin, α-lipotropin, β-endorphin, and α-melanocyte-stimulating hormone by ectopic ACTH-producing tumors of pancreatic and pulmonary origin.[10, 11]

The human placenta also possesses the proopiomelanocortin system, but the processing is similar to that in the rodent intermediate lobe, in that ACTH and β-lipotropin appear to be further processed to α-melanocyte-stimulating hormone–like and β-endorphin–like peptides, respectively.[12]

Immunoreactive β-endorphin is detected in human semen.[13] Subsequent experiments indicated the presence of the proopiomelanocortin system in rat testes and its processing, probably by Leydig cells, mainly into ACTH and β-endorphin.[14] In the human ovary, we have detected the presence of β-endorphin in the stromal cells (unpublished observation).

Proenkephalins were initially thought to be the unique common precursors for Met-enkephalin and Leu-enkephalin. However, with the recent discovery of the precursor common for dynorphin and the neoendorphins, existence of separate proenkephalins A and B was realized.[4] The structure of both bovine and human proenkephalin A has been elucidated by recombinant DNA techniques.[5, 15]

Met- and Leu-enkephalin, Met-enkephalin-Arg^6-Phe^7 and Met-enkephalin-Arg^6-Gly^7-Leu^8 are derived from proenkephalin A. This precursor is produced in the adrenal medulla, the brain, and the gastrointestinal tract.[16, 17] The processing of proenkephalin A differs in the brain and the adrenal medulla; it is almost complete in the brain, yielding four molecules of Met-enkephalin and one each of Leu-enkephalin, Met-enkephalin-Arg^6-Phe, and Met-enkephalin-Arg^6-Gly^7-Leu.[8] On the other hand, the processing is limited in the adrenal medulla, yielding a variety of intermediate forms. In the bovine adrenal medulla, however, release of all four peptides together with epinephrine and norepinephrine has been observed.[16]

The processing of proenkephalin B is only partially understood. It is uncertain whether Leu-enkephalin is produced by this precursor molecule. The unique feature of the dynorphins, the major product of proenkephalin B, is their high analgesic potency and their behavioral effects.

In summary, opioid peptides are derived from three sets of precursor peptide systems, which have different distributions and functions in the body. Proopiomelanocortin exists in the pituitary gland, brain, sympathetic nervous system, adrenal medulla, gastrointestinal tract, male reproductive tract, and placenta, with the highest concentration found in the pituitary gland. Proenkephalin A is present in the adrenal medulla in the highest concentration, but it is also present in the posterior pituitary gland, brain, spinal cord, and gastrointestinal tract. Proenkephalin B is found in the neurointermediate lobe of the pituitary gland (bovine) in its highest concentration, and in the human brain and gastrointestinal tract.

Multiple opiate receptors. The opiates induce a large variety of pharmacologic responses by interacting with various stereospecific sites in the central nervous system and in certain peripheral tissues. The pharmacologic characteristics of these receptors have been investigated in detail by means of assays that involved measurement of the contraction of electrically stimulated muscle from the guinea pig ileum and mouse vas deferens.[18] In addition, considerable progress in elucidating the molecular basis of opiate action has been achieved with the introduction of biochemical assays in which drug-receptor interactions are monitored in membrane preparations in which radioactively labeled opiates are used.[19]

One class of receptors, called morphine or μ-receptors, preferentially binds opiates. The other class, called enkephalin or δ-receptors, preferentially binds enkephalin. In membrane preparations from whole rat brain there are twice as many receptors which preferentially bind morphine (μ-receptors) as those which preferentially bind enkephalin (δ-receptors).[20] The regional distribution of receptors for morphine and enkephalin within the central nervous system has been mapped[21]: (1) The cerebral cortex and striatum contain about equal numbers of both types of receptors; (2) the limbic system, hippocampus, and brain stem contain twice as many morphine receptors as enkephalin receptors; (3) in the thalamus and hypothalamus, the ratio of morphine to enkephalin receptors rises to four. It should be noted that opiate antagonists, such as naloxone and naltrexone, have a 10 to 20 times higher affinity for morphine receptors than for enkephalin receptors.

Ketocyclazocine, a κ-agonist, binds to a class of receptors which are insensitive to naloxone.[22] Dynorphin represents the natural ligand, but both enkephalin and morphine possess high binding affinity to the putative κ-receptor. The κ-agonists are also known to cause dysphoria and hallucination in man, whereas morphine causes euphoria.

The multiplicity of opioid receptors is paralleled by the existence of a series of different endogenous opioid peptides which possess differing selectivity for particular types of receptors. To date, elucidation of various receptors (and opioid peptides) with specific opioid action have not yielded a simple relationship between them.

Opioidergic control of secretion of gonadotropin-releasing hormone. Rasmussen et al.[23] demonstrated that the midgestation human fetal mediobasal hypothalamus can respond to in vitro administration of the opiate receptor antagonist naloxone with an increased release of gonadotropin-releasing hormone, and that this response to naloxone can be inhibited by simultaneous administration of equimolar β-endorphin. These findings provide evidence that the observed endogenous opiate inhibition of secretion of luteinizing hormone in humans is mediated by suppression of hypothalamic release of gonadotropin-releasing hormone.

The in vitro perfusion method of investigating the regulation of release of gonadotropin-releasing hormone from the rat mediobasal hypothalamus has been thoroughly characterized by our laboratory. The release pattern of the human fetal mediobasal hypothalamus in this study (high initial rate declining to a lower basal rate) was similar to that observed in the studies with rat mediobasal hypothalamus. The occasional fluctuations in basal release rate may reflect an episodic pattern of neurosecretion of gonadotropin-releasing hormone. Functional viability of the fetal tissue was confirmed by the rapid release of gonadotropin-releasing hormone in response to a depolarizing dose of potassium chloride after 5 hours of perfusion, with no response to equimolar administration of sodium chloride. The proportional increase in the release of gonadotropin-releasing hormone in response to naloxone and potassium chloride was similar to that achieved with rat mediobasal hypothalamus.[24]

Although the neuroendocrine activity of the fetal hypothalamus may differ from that of the normal adult hypothalamus, compelling evidence indicates that the human hypothalamic-pituitary system forms a well-differentiated functional unit by midgestation (for reviews, see references 25, 26, and 27). Particularly relevant to our present study is the identification of β-endorphin in neuronal elements of the arcuate-median eminence unit of the human fetal hypothalamus.[28] These neuroanatomic and functional data permit a meaningful interpretation of our present findings. Recently, we confirmed these findings in adult hypothalamic tissue. The increased release of hypothalamic gonadotropin-releasing hormone in response to the opiate receptor blockade is congruent with the demonstration by Schulz et al.[29] that an increase in circulating luteinizing hormone followed in vivo administration of antiserum to β-endorphin into the arcuate nucleus of immature female rats. The ability of exogenous β-endorphin to suppress naloxone-induced release of gonadotropin-releasing hormone by the mediobasal hypothalamus observed in our study supports the contention that interactions of the agonist and antagonist occurred at the level of opiate receptors and is in keeping with the high affinity of β-endorphin in the displacing of naloxone from μ-receptors.

Influence of ovarian steroid milieu on opioidergic control of gonadotropin secretion. That gonadal steroids modify endogenous opiate activity is suggested by the finding that naloxone induces an increased frequency and amplitude of pulsatile release of luteinizing hormone during late follicular and midluteal phases, but not in the early follicular phase of the menstrual cycle.[30, 31] Furthermore, we have observed that the elevated levels of gonadotropin in postmenopausal women failed to respond to the inhibitory effect of β-endorphin.[32] Of interest is the fact that the same dose of β-endorphin (2.5 mg) induced significant suppression of luteinizing hormone in both normal men and women with normal menstrual cycles.[33] Grossman et al.[34] reported that a Met-enkephalin analogue induced suppression of levels of luteinizing hormone in postmenopausal women. Although the reason for this discrepancy is uncertain, differences in the inhibitory potencies and receptor binding (μ-receptors versus δ-receptors) of these two peptides in postmenopausal women may be involved. This former possibility is compatible with our finding that the dose of β-endorphin used was sufficient to exert a central effect, as evidenced by an increment in the release of prolactin. Furthermore, infusion of naloxone also failed to modify the pulsatile pattern of release of gonadotropin in postmenopausal women.[32] The inability of an enkephalin analogue (FK 33-824) to suppress the secretion of luteinizing hormone after gonadectomy in rats[35] and the experimental evidence that suggests that β-endorphin and Met-enkephalin may function differently in the hypothalamic control of secretion of luteinizing hormone[29] support our finding of the uncoupling of opioidergic influence on gonadotropin-releasing hormone activity in the absence of ovarian steroid feedback, as in postmenopausal women.

Additional evidence that endogenous hypothalamic opioid activity is modulated by ovarian steroids is afforded by the work in monkeys. Wehrenberg et al.[36] and Wardlaw et al.[37] reported that concentrations of β-endorphin in the hypophyseal portal blood were nearly undetectable in monkeys during the early follicular phase of the menstrual cycle and after ovariectomy, but were markedly elevated after treatment with estrogen and progesterone. In rats, Van Vugt et al.[38] and Bhanot and Wilkinson[35] showed that the inhibitory effect of opioids on the secretion of luteinizing hormone was eliminated by gonadectomy and restored by the administration of gonadal steroids. Thus the lack of response of luteinizing hormone to both naloxone and β-endorphin in postmenopausal women may be an expression of markedly reduced endogenous opiate receptor activity. The disappearance of ovarian steroid feedback may account for the diminished hypothalamic opioid peptide inhibition of release of gonadotropin-releasing hormone and could be functionally related to the increased frequency of pulses of luteinizing hormone and the unrestrained secretion of gonadotropin in postmenopausal women. By inference, the negative feedback effect of ovarian steroids on the secretion of gonadotropin may, in part, be mediated through an increase in the opioidergic mechanism.

Evidence for an increased opioidergic mechanism in certain hypogonadotropic states. It is now established that most, if not all, functional hypogonadotropic states are due to the absence or marked attenuation of gonadotropin-releasing hormone–mediated pulsatile release of pituitary gonadotropin (see review, reference 39). That endogenous opioids inhibit pulsatile frequency and amplitude of release of gonadotropin-releasing hormone by the mediobasal hypothalamus is compelling (see above). Thus the low amplitude of pulsatile secretion of luteinizing hormone in patients with hyperprolactinemia and functional hypothalamic amenorrhea may be causally related, at least in part, to an increased endogenous opioid inhibition of release of gonadotropin-releasing hormone. Indeed, an increase in luteinizing hormone pulses during infusion of naloxone (1.6 mg/hr) has been demonstrated in these two hypogonadotropic states.[40, 41] Similar observations were made in patients with weight loss–related amenorrhea.[42] This and related issues have recently been reviewed by Grossman and Rees.[43]

The hypogonadotropic state of the postpartum period provides a physiologic model for the study of endogenous opioid activity. Several lines of evidence suggest that the massive increase in sex steroids during pregnancy may induce hypothalamic suppression of gonadotropin-releasing hormone, and that the prolonged deprivation of endogenous gonadotropin-releasing hormone may extend to the puerperium to account for the unresponsiveness to exogenous gonadotropin-releasing hormone and hypogonadotropinism. A direct inhibitory effect on the gonadotrope by high levels of sex steroids may also occur. Recovery, either spontaneous or prematurely activated by the administration of gonadotropin-releasing hormone, follows a predictable sequence of preferential secretion of follicle-stimulating hormone and then luteinizing hormone, an observation closely resembling that of the prepubertal state (see review, reference 44).

Although the levels of gonadotropin did not change in response to naloxone (and gonadotropin-releasing hormone) 10 days post partum, the infusion of naloxone induced significant increments in the serum levels of both follicle-stimulating hormone and luteinizing hormone in all subsequent studies. There were differences in the relative increases in follicle-stimulating hormone and luteinizing hormone as the puerperium progressed. Preferential release of follicle-stimulating hormone was observed on days 13 to 15 and resulted in serum levels threefold greater than those for luteinizing hormone. This difference progressively diminished (days 17 to 20) and was found to be reversed on day 25. Gonadotropin-releasing hormone (10 μg pulse) induced similar trends in the release of gonadotropin in terms of both magnitude and time course. Furthermore, a significant ($p < 0.01$) positive linear correlation was found between the gonadotropin peak during naloxone and that after gonadotropin-releasing hormone ($r = 0.636$ for luteinizing hormone and $r = 0.722$ for follicle-stimulating hormone). These observations support the idea of an increased opioid inhibition of the secretion of gonadotropin-releasing hormone accountable for the hypogonadotropinism of the puerperium.[45]

In summary, substantial evidence now exists to indicate that the endogenous hypothalamic opioidergic mechanism(s) represent one of the important controlling systems for the release of gonadotropin-releasing hormone. Modulations of frequency and amplitude of gonadotropin-releasing hormone secretory activity appear to be mediated through an inhibitory action of endogenous opioids, and the functional coupling of the opioidergic and gonadotropin-releasing hormone systems is an event dependent on ovarian steroids.

Endogenous opioids on secretion of prolactin. Administration of opiate peptides have been shown to stimulate the release of prolactin in all species studied, including man.[33, 46, 47] Experimental evidence indicates that the opioidergic control of the secretion of prolactin is mediated through its inhibition of dopamine turnover[48, 49] and release[50, 51] by the tuberoinfundibular neurons. If this functional relationship operates in vivo, and if the naloxone-sensitive opiate receptor is involved, a decrement in the release of prolactin should occur subsequent to opiate receptor blockade by naloxone. Although this phenomenon has been demonstrated in rats[52] and monkeys,[53, 54] available evidence in man indicates otherwise. With the exception of one study in which large doses of naloxone (15 mg intravenously) almost completely abolished the rise in prolactin during vigorous exercise tasks in professional athletes,[55] the administration of naloxone at different dose regimens does not appear to affect either basal[42, 56-63] release of prolactin or that induced by sleep,[57, 59] exercise,[64, 65] hypoglycemia,[63] or gastroscopy.[60] In addition, high doses of naloxone do not suppress puerperal hyperprolactinemia,[34] suckling-stimulated release of prolactin, or hyperprolactinemia due to pituitary microadenoma.[66] However, the functional relationship between the opioidergic control of and the well-known stimulatory effect of estrogens and progestins on the secretion of prolactin[67, 68] has not been investigated in any species. We have addressed this issue by examining the responses of prolactin to infusion of naloxone during three phases of the menstrual cycle and in hypogonadal women. In addition, comparisons were made between changes in the secretion of prolactin and the well-established pulsatile release of luteinizing hormone in response to infusion of naloxone as a reference of opioidergic control systems.

Although no discernible changes in the levels of prolactin were observed in women during the early follicular phase, infusion of naloxone induced a prompt and sustained release of prolactin in all women during the late follicular and luteal phases, with the mean (±SE) peak increments being 16.9 ± 5.3 and 9.7 ± 3.2, respectively.[69]

These findings prompted us to examine the pulsatile response of prolactin to a longer duration (8 hours) of infusion of naloxone during the luteal phase of five women with normal menstrual cycles and in five hypogonadal women.[69] Control infusions of saline solution were performed on a separate day for the same duration and at the same time of day. In the hypogonadal women, the frequencies of pulsatile activity of prolactin during the 8-hour infusions of naloxone (2.6 ± 0.7 pulses) and of saline solution (2.6 ± 0.5 pulses) were similar. In contrast, infusion of naloxone in the women during the midluteal phase elicited an unequivocal increase in the magnitude and frequency of the prolactin pulse (3.4 versus 1.6/8 hours, $p \leq 0.001$) in all five experiments. On the other hand, in women during the late luteal phase ($n = 3$), there was no consistent pattern of release of prolactin in response to naloxone. A positive linear correlation between the integrated prolactin response to naloxone and circulating levels of estradiol ($r = 0.62$, $p < 0.05$) and progesterone ($r = 0.95$, $p < 0.01$) was found. Thus the pulsatile activity of prolactin was increased when levels of progesterone were high (midluteal) and virtually absent when levels of progesterone were low (late luteal).

Since we previously observed that the infusion of naloxone also induces an increase in the pulsatile activity of luteinizing hormone in women during the luteal phase, the relationship of prolactin and luteinizing hormone pulses was analyzed. We found that luteinizing hormone and prolactin pulses occur simultaneously during infusion of naloxone. A significant increase in the number of luteinizing hormone ($p < 0.001$) and prolactin ($p < 0.05$) pulses during infusion of naloxone in comparison to infusion of saline solution was observed. In addition, the percentage of concomitant pulses was increased in every case, and the mean concomitancy was significantly ($p < 0.001$) greater during naloxone (96%) than during saline solution control (36%).[69]

Thus a stimulatory role of endogenous opioids in the control of secretion of prolactin in men, in contrast to the rat, does not appear to be operative. Instead, there is seemingly an inhibitory role of endogenous opioids on the secretion of prolactin which become functional only in the presence of high levels of ovarian steroids.

The neuroendocrine mechanism(s) to account for the ovarian steroid–dependent, naloxone-induced release of prolactin is unclear. A remarkable augmentation of pulsatile release of prolactin in synchrony with luteinizing hormone subsequent to opiate-receptor blockade observed in women during the midluteal phase suggests that estradiol and progesterone, through their feedback action on the hypothalamic-pituitary complex, may serve to couple a common neuroendocrine mechanism that involves opioidergic control of the secretion of both luteinizing hormone and prolactin. Several lines of evidence supporting hypothalamic gonadotropin-releasing hormone may subserve such a functional link. First, we have demonstrated that the infusion of very small amounts of gonadotropin-releasing hormone (0.2 μg/min) consistently increases the secretion of prolactin in women with normal cycles and in hypogonadal women.[70] Stimulation of the secretion of prolactin was also induced by subcutaneous injection of 50 μg doses of gonadotropin-releasing hormone agonist.[70, 71] In intact and castrated men, gonadotropin-releasing hormone stimulates the release of prolactin, which is augmented by pretreatment with estrogen.[72] Thus gonadotropin-releasing hormone may be considered to be a putative prolactin-releasing factor. Second, a synchronized pulsatile release of prolactin and luteinizing hormone has been described in women with normal cycles[73, 74] and in hypogonadal women.[75] As indicated earlier, a close parallelism appears to exist between prolactin and luteinizing hormone responses to naloxone, with an increase in pulsatile activity during a high estrogen and progesterone milieu but not in women during the early follicular phase and in hypogonadal women. Finally, the release of luteinizing hormone in response to naloxone is mediated by gonadotropin-releasing hormone, as evidenced by the rapid release of gonadotropin-releasing hormone (>100%) by the human mediobasal hypothalamus upon exposure to naloxone in a perifusion system,[23] and the abolishment of naloxone-induced pulsatile release of luteinizing hormone by a gonadotropin-releasing hormone antagonist (unpublished observation).

Thus one may postulate that the paradoxical release of prolactin in response to naloxone is occasioned by the pulsatile release of endogenous gonadotropin-releasing hormone, thereby inducing the release of both luteinizing hormone and prolactin. The action could be mediated through the marked increase in β-endorphin concentrations in the hypophyseal portal blood, which during the luteal phase of the cycle may function to suppress the inhibitory action of dopamine on the release of prolactin at the level of the pituitary gland, as demonstrated in vitro.[76] The most likely possibility is the recent in vitro demonstration that the prolactin-releasing effect of gonadotropin-releasing hormone is mediated by a paracrine effect from gonadotrope to lactotrope[77] and that the lactotrope differentiation may depend partly on the stimulatory effect of gonadotropin-releasing hormone.[78] Collectively, these observations provide new insights for future investigation of steroid modulation of opioidergic control of the secretion of gonadotropin-releasing hormone and prolactin in man.

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Discussion

Dr. Charles D. Kimball, Seattle, Washington. The report by Yen et al. on opioid peptide regulation of gonadotropin-releasing hormone and prolactin hormone constitutes an essential link in the chain of evidence whereby the age-old mysteries of reproductive physiology and sexual behavior are gradually being unraveled. Yen et al. have contributed a prodigious amount of hard-core information on opioid peptides during the past few years, and I think that it is a distinct privilege to discuss their report to this Society.

The link between feelings, brain centers, and cyclic gonadal function has been postulated for several decades. Now Yen et al. have demonstrated the cybernetic mechanism by which increasing amounts of opioid hormone evoked by ovarian steroids during the luteal phase of the menstrual cycle slow the rate and increase the amplitude of the pulselike spurts of gonadotropin-releasing hormone and luteinizing hormones that regulate ovarian function, much like tetraethyl lead slows the combustion and increases the power of gasoline. The increased production of opioid peptides secreted by hypothalamic nerve cells during the progestation phase also blocks release of dopamine into pituitary portal channels and stimulates production of prolactin, which is held in tonic inhibition by dopamine. The paradoxical finding by Yen et al. that naloxone during the luteal phase stimulates rather than blocks prolactin in women could be due to the compensatory overreaction of enkephalin and dynorphin opioids that also suppress dopamine and are not blocked by the naloxone displacement of β-endorphin on μ-receptors, thereby indicating the broad scope of opioidergic mechanisms in humans, in contradistinction to other species.

Clarification of these opioidergic mechanisms enables rational explanation of many clinical enigmas and problems in patients. For example, it is known that increasing sodium ion molarity suppresses opioid receptor binding affinity and reduces analgesic potency of both endogenous opioid hormones and exogenous opiate alkaloids, whereas at the same time receptor affinity for naloxone (Narcan), which specifically blocks morphine receptors, is increased. Thus, the well-known tendency for salt retention during the progestational phase can explain decreased tolerance to pain, mastodynia, cephalalgia, backache, premenstrual tension, etc., because the comforting effects of the steroid-enhanced production of opioid hormones would be impaired by reduced μ-receptor affinity.

Inasmuch as narcotic opiates are known to dominate the thoughts, moods, and behaviors of addicts, it seems quite possible that opioid hormones elevated by reproduction and survival functions can reward and reinforce moods, thoughts, and behavior patterns, as well as motivate specific affectional interdependency (i.e., love), courtship, mating, birthing, and nurturing of offspring. Accepting the fact that all habitual behavior must be continually reinforced by some sort of reward, it becomes apparent that our feelings and appetite for opioid hormones could dominate our behavior patterns rather than will power, logic, or good intentions as we would like to believe. Thus opioid peptides that normally evoke prolactin and suppress gonadotropin-releasing hormone and luteinizing hormone in the puerperium reinforce breast-feeding, which is considered by many women to be a pleasurable and rewarding experience. As reported at our meeting last year, low blood levels of immunoreactive β-endorphin during labor tend to presage postpartum blues.

Other clinical interpretations of the data of Yen et al. can be found in the precipitate drop in both ovarian steroids and opioid hormones at menstruation and the deficiency of these hormones in menopause. Dysmenorrhea, abdominal cramps, emotional and vasomotor instability, dysphoria, and mood irritability all mimic opium withdrawal symptoms, and all are promptly relieved by codeine or other opium alkaloids. Nausea of early pregnancy may be caused by steroid-induced elevation of opioid hormones in cerebrospinal fluid that stimulate the area postrema neurons in sedentary women naive to alcohol and other modalities that elevate opioid peptides.

Briefly looking toward the future by way of published research developments in molecular biology and neuroendocrinology, we now believe certainly that opioidergic mechanisms play a prominent part in memory and learning functions, feeding patterns and appetite satiety, mother-infant affect and character formation, mood functions, proneness to drug dependency, and mental illness. Practicing physicians and students concerned with reproductive processes and infant health and behavioral medicine have common cause to explore the influence exerted by opioid hormones, their precursor enzymes, and protein synthesis on gene expression and function of neural tissues during embryonic and fetal life, as well as in infancy and childhood.

President Rust, our society is indeed fortunate to include on its roster members who are able to produce and share seminal basic science information upon which clinical advances in the care of patients depend.

Dr. Tawfik Rizkallah, Phoenix, Arizona. Dr. Kimball pointed out that endorphins are increased in the luteal phase of the menstrual cycle and made the assumption that the increase in the serum concentration of endorphins is secondary to an increase in the production of progesterone. I hope that Yen et al. have examined this question and attempted to elucidate whether this increase in endorphins is due to progesterone alone or whether other gonadal steroids exert either a positive or negative effect on the production of endorphins. Patients who are hypogonadal or patients who suffer from polycystic ovarian disease may be a model for the testing of the authors' hypothesis. Dr. Kimball also made the assumption that changes in the mood and the depression seen premenstrually in some patients may be due to a decrease in serum progesterone. Before accepting such an assumption, we have to have experimental data that show a direct dose response correlation between progesterone and endorphins.

Erratum

In the March 15, 1985, issue of the Journal, in the article by Cotton et al., on page 762, entitled "Cardiovascular alterations in severe pregnancy-induced hypertension: Relationship of central venous pressure to pulmonary capillary wedge pressure," there is an error in Table I. Under the heading "Pulmonary capillary wedge pressure (mm Hg)" and the subheading "Minimum," line number 10, the number "3" should have been "8."

ITEMS

Announcements of major meetings and other significant activities must be received at least 8 weeks before the desired month of publication. All announcements carry a charge of $45.00 U.S. and the fee must accompany the request to publish. Information will be limited to title of meeting, date, place, and an address to obtain further information. Send announcements and payment, payable to this JOURNAL, to The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63146.

Teratology—Principles and Clinical Applications, July 27–August 1, 1985, Snowmass, Colorado. For further information contact: Lee Pickles, CME, Scott & White, Temple, TX 76508. Tel.: (817) 774-4083.

Three Postgraduate Gynecology Courses: Advanced Gynecologic Oncology, September 7-9, 1985; Advances in Gynecology, September 10-12, 1985; Reproductive Endocrinology, September 13-16, 1985; Massachusetts General Hospital, Boston, Massachusetts. Contact: Harvard Medical School, Department of Continuing Education, 25 Shattuck St., Boston, MA 02115.

Perinatal Malpractice, September 12-13, 1985, Northwestern University Medical School Alumni Center for Continuing Education, 301 E. Chicago Ave., Chicago, IL 60611. For further information contact: Paula Puntenny, Director, Alumni Center for Continuing Education, Northwestern University Medical School, 301 E. Chicago Ave., Chicago, IL 60611. Tel.: (312) 908-8533.

Intensive Board Review Course in Reproductive Endocrinology, September 13-16, 1985, Massachusetts General Hospital, Boston, Massachusetts. Contact: Dr. William F. Crowley, Jr., Vincent Research Laboratories, Massachusetts General Hospital, Boston, MA 02114.

London and Paris Fall Ultrasound—Obstetrics and Gynecology, London, England, September 20-25, 1985; Paris, France, September 25-29, 1985. For further information contact: Secretary, Fall Ultrasound Symposia, Medical Seminars International, West Park Medical Office Building, 22135 Roscoe Blvd., #104, Canoga Park, CA 91304. Tel.: (818) 340-0580, ext. 280.

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Abbott Laboratories
Ogen 19A,20A,21A

Baystate Medical Center
Opportunity Available 23A

Central Ohio Medical Group
Opportunity Available 23A

Merck Sharp & Dohme
Mefoxin .... Second Cover,1A,2A

Miles Pharmaceuticals
Mycelex-G 500 .... 13A,14A,15A,16A

Parke-Davis
Norlestrin 9A,10A

Pennsylvania Hospital
Fellowship 23A

San Joaquin General Hospital
Opportunity Available 24A

Southwest Community Health Services
Opportunity Available 24A

SUNY at Stony Brook
Opportunity Available 16A

Syntex Laboratories, Inc.
Norinyl 17A,18A

Womens Medical Center of America
Opportunity Available 23A

Wyeth Laboratories
Triphasil .... Third Cover,Fourth Cover

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IN BRIEF:

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Indications and Usage—TRIPHASIL* is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

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Warnings

> **Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.**
>
> The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with the use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of s) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effective- s of method. The study concluded that mortality associated with all methods of birth control is low and below associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is ciated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease ociated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and atient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebi- s, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric rombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6- d increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OC's hould be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism prolonged immobilization.

ERSISTENCE OF RISK OF VASCULAR DISORDERS—Findings from one study in Britain involving cerebrovascular disease and another in the U.S. concerning MI suggest an increased risk of these conditions in users of OC's persists after discontinuation of the OC's. In the British study, risk of cerebrovascular disease remained levated in former OC users for at least 6 years after discontinuation. In the U.S. study, increased risk of MI rsisted for at least 9 years in women 40 to 49 years old who had used OC's for 5 or more years. Findings in oth studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases bmitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. ases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, ycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No vidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or ith breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they lect to use OC's.

. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study howed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although enign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been ported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk eing much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously amage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, ave increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk as been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's urther enhance risk of developing this type of malignancy, such patients should be monitored with particular care if ey elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes f the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract lthough similar data are not available with use of other estrogens, it cannot be presumed they would not induce imilar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been ported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold ncrease in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few day Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evi from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If th patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time o missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of beco pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinic recommend 3 months, although no precise information is available on which to base this. The administration c progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of O and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed on OC's. Increases in triglycerides and total phospholipids have been observed in patients on OC's. Three stud were performed with Triphasil and no significant alterations in lipid metabolism were noted except for a slight increase in triglyceride levels in 1 study. Clinical significance of these findings remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some wome hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women w hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in increases, however, with longer exposure, and in the 5th year of use is $2\frac{1}{2}$ to 3 times the reported prevalence 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hyperte sion that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurre persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patient discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional cause should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time o change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potenti useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young won without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuir OC's. Women with these preexisting problems should be advised of this possibility and encouraged to use othe methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity anc quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until i has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should r prescribed for longer than 1 year without another physical examination and Pap smear.

2. Under influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depres recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with carel monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorc migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administ with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a wo becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency a complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing (

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measure protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, refle the elevated TBG; free T4 concentration is unaltered.

d. Decreased pregnanediol excretion.

e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated v concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phe sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings section for information on carcinogenesis.

Pregnancy—Category X. See Contraindications, Warnings

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemo rhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an ass ciation between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Na and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of pati during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuan treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and se tion; change in weight (increase or decrease); change in cervical erosion and cervical secretion, possible dimin in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiom omata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses. The following adverse reactions have been report users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, catara changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsu tism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration—For maximum contraceptive effectiveness, Triphasil must be taken exactly as dire and at intervals not over 24 hours. (If Triphasil is first taken later than first day of first menstrual cycle of medica or postpartum, contraceptive reliance should not be placed on it until after the first 7 consecutive days of use. Possibility of ovulation and conception prior to initiation of medication should be considered.)

Anytime patient misses 1 or 2 brown, white or light-yellow tablets, she should also use another contraceptive method until she has taken a tablet daily for 7 consecutive days.

For full details on dosage and administration see prescribing information in package insert.

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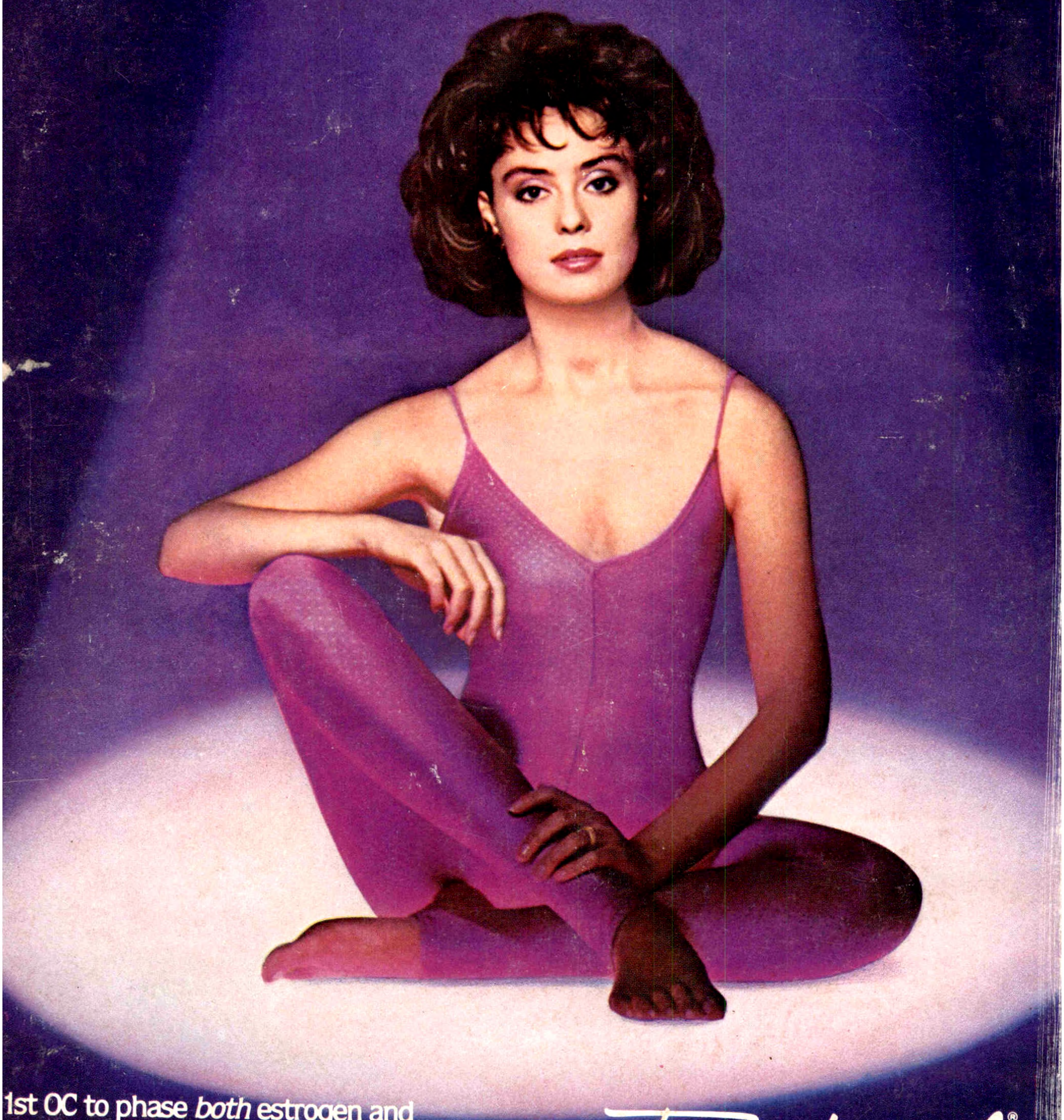

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- 1st triphasic to start dose 1 on *Her* Day 1 ...easier to remember

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See important information on adjacent pa